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<b>Applicant</b> OHKAWA, Shigenori et al	

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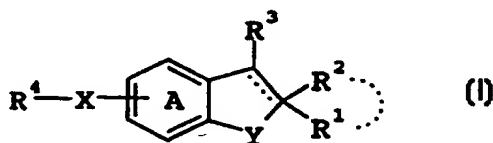
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: HETEROCYCLIC COMPOUNDS, THEIR PRODUCTION AND USE



(I)

**(57) Abstract**

A compound of formula (I): wherein R<sup>1</sup> and R<sup>2</sup> each is H or a hydrocarbon group which may be substituted, or R<sup>1</sup> and R<sup>2</sup> form a 3- to 8-membered carbo or heterocyclic ring which may be substituted; R<sup>3</sup> is H, a lower alkyl which may be substituted or an aromatic group which may be substituted; R<sup>4</sup> is (1) an aromatic group which may be substituted, (2) an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (3) an acyl; X and Y each is oxygen or sulfur which may be oxidized; and ring A is a benzene ring which may be further substituted, or a salt thereof, is useful for an agent for suppressing neurodegeneration.

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## DESCRIPTION

## Heterocyclic Compounds, Their Production and Use

TECHNICAL FIELD

5           The present invention relates to heterocyclic compounds, their production and use, and the compounds suppress cell toxicities caused by  $\beta$ -amyloid protein, protect nerve cell, and are useful for preventing and/or treating neurodegenerative diseases by  
10       protecting nerve cell from other inducers of cell death.

BACKGROUND ART

          Neurodegenerative diseases are progressive disorders that cause fatal damage of nerve cell death.  
15       As principal neurodegenerative diseases, known are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's chorea, peripheral nervous system disorders such as typically diabetic neuropathy, etc. Most of those are related to  
20       aging, and, in fact, cases that present the symptoms of those diseases increase with aging. However, middle-aged and even young-aged cases may often present the symptoms of those diseases.

          As a result of studies relating to the structure and function of brains, the roles of neurotransmitters and neurotrophins are being gradually clarified, but  
25       most part of the causes of neurodegenerative diseases are still unknown. Only for Parkinson's disease, the relation between it and a specific neurotransmitter, dopamine has been clarified. L-dopa, which is a  
30       precursor of dopamine, is used as a medicine for Parkinson's disease. L-dopa relieves the neuropathic manifestation of Parkinson's disease, and maintains function. However, L-dopa could not suppress the  
35       progress of neurodegeneration in cases of Parkinson's disease, and it gradually loses its potency with the



progress of the manifestation of the disease, or that is, with the degeneration and death of dopamine-based nerve cells. Alzheimer's disease results in the degeneration and death of many types of nerve cells such as acetylcholine-based nerve cells and monoamine-based nerve cells. For this disease, some cholinesterase inhibitors are commercially available and some others are in the development stage. However, those are still within the range of symptomatic treatment for temporarily relieving the neuropathic manifestation of Alzheimer's disease, like L-dopa for Parkinson's disease.

As has been mentioned above, no medicines have been reported for protecting nerve cells from the toxicity of factors causing cell death thereby to suppress the progress of neurodegenerative diseases including Alzheimer's disease and Parkinson's disease.

It is said that the cell death in neurodegenerative diseases is caused by the toxicity of factors that are intrinsic to the respective diseases. For Alzheimer's disease, for example, it is believed that the intrinsic  $\beta$ -amyloid in the disease is a factor to cause cell death.  $\beta$ -amyloid is a protein seen in the brains of cases of Alzheimer's disease, and this constitutes senile lentigines that are characteristic of the disease in neuropathology, and is composed of from 40 to 43 amino acids. It has been clarified that, when  $\beta$ -amyloid is added to the primary culture of hippocampus nerve cells, this kills the cells (see Science, Vol. 245, pp. 417-420, 1989); and it has been reported that the coagulation of  $\beta$ -amyloid is indispensable for the expression of its toxicity (see Neurobiology of Aging, Vol. 13, pp. 587-590, 1992; and Journal of Molecular Biology, Vol. 218, pp. 149-163, 1991). For the toxicity expression mechanism of  $\beta$ -

amyloid, the following (1) to (4) may be taken into consideration: (1)  $\beta$ -amyloid forms ion channels, through which calcium ions run into nerve cells. (2)  $\beta$ -amyloid promotes the generation of free radicals.

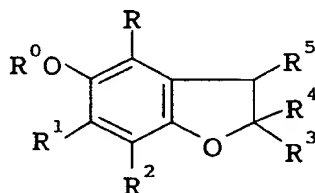
5 (3)  $\beta$ -amyloid activates tau-protein kinase I (TPK-I) whereby phosphorylation of tau is promoted. (4)  $\beta$ -amyloid activates microglia, which thereby secretes neurotoxin. However, no one has as yet obtained the conclusion.

10 Recently, it has been clarified that neurotrophins such as IGF-1 (insulin-like growth factor) and NGF (nerve growth factor) inhibit the apoptosis of nerve cells by  $\beta$ -amyloid or the like, and that, for its mechanism, the apoptosis inhibition is related to the  
15 inhibition of TPK-I/GSK-3 $\beta$  (glycogen synthase kinase 3) through activation of PI-3 kinase (see J. Neurosci., Vol. 11, pp. 2552-2563, 1991; Science, Vol. 267, pp. 2003-2006, 1995; and J. Biol. Chem., Vol. 272, pp. 154-161, 1997). When PI-3 kinase is inhibited by  $\beta$ -amyloid  
20 and TPK-I/GSK-3 $\beta$  is activated, then pyruvate dehydrogenase (PDH) is inhibited, while having an influence on the synthesis of acetylcholine, to thereby lower the acetylcholine content. This is supported by the decrease in the acetylcholine content of the brains  
25 of cases of Alzheimer's disease. On the contrary, when PI-3 kinase is activated, then it is expected that not only the nerve cell death is prevented but also the intracerebral acetylcholine content is increased to improve the nervous system condition. In addition, it  
30 is also expected that the inhibition of TPK-I/GSK-3 $\beta$  results in the increase in the intracerebral glucose utilization which is lowered in cases of Alzheimer's disease (see J. Biol. Chem., Vol. 269, pp. 3568-3573, 1994; and Endocrinology, Vol. 125, pp. 314-320, 1989).

Accordingly, low-molecular compounds having good permeability to the brain and having neurotrophic action may inhibit nerve cell death in cases of neurodegenerative diseases such as Alzheimer's disease, while improving the nervous system condition in those cases.

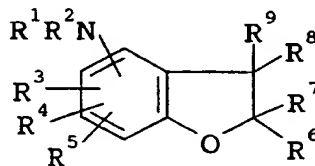
Known are the following dihydrobenzofuran compounds which are effective for neurodegenerative diseases (e.g., Parkinson's disease, Alzheimer's disease, etc.).

1) A compound of the formula:



wherein R is a lower alkyl, R<sup>0</sup> is hydrogen or an acyl; R<sup>1</sup> and R<sup>2</sup> are the same or different and are a lower alkyl which may be substituted, or R<sup>1</sup> and R<sup>2</sup>, taken together, are a butadienylene which may be substituted; R<sup>3</sup> and R<sup>4</sup> each is hydrogen or an alkyl which may be substituted, or R<sup>3</sup> and R<sup>4</sup>, taken together, are a polymethylene; R<sup>5</sup> is a lower alkyl, an aromatic group or heterocyclic group which may be substituted (EP-A-273647, JP-A-1-272578).

2) A compound of the formula:

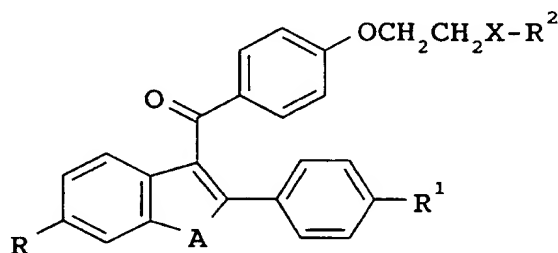


wherein R<sup>1</sup> and R<sup>2</sup> are the same or different and are a hydrogen atom, an acyl, an alkoxy carbonyl, an optionally substituted aliphatic group or an optionally substituted aromatic group; R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are the same or different and are an optionally acylated hydroxy, an optionally substituted amino, an optionally substituted

alkoxy or an optionally substituted aliphatic group, or two of  $R^3$ ,  $R^4$  and  $R^5$  may be linked together to form an optionally substituted carbocyclic group;  $R^6$  and  $R^7$  are the same or different and are an optionally substituted aliphatic group, provided that at least one of  $R^6$  and  $R^7$  has methylene at  $\alpha$ -position; and  $R^8$  and  $R^9$  are the same or different and are a hydrogen atom, an optionally substituted aliphatic group or an optionally substituted aromatic group, or a salt thereof (EP-A-483772, JP-A-5-140142).

Also known are the following benzofuran compounds and dihydrobenzofuran compounds.

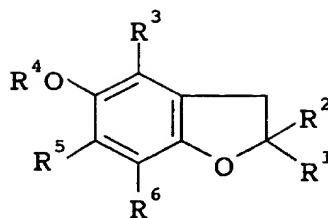
3) A compound of the formula:



wherein A is  $-O-$ ,  $-S(O)m-$ ,  $-N(R^{11})-$ ,  $-CH_2CH_2-$ , or  $-CH=CH-$ ; m is 0, 1, or 2; X is a bond or  $C_{1-4}$  alkylidenyl;  $R^2$  is a group of the formula:  $-NR^4R^5$  wherein  $R^4$  and  $R^5$  are independently  $C_{1-6}$  alkyl, etc.); R is hydroxy, halo,  $C_{3-8}$  cycloalkyl,  $C_{2-7}$  alkanoyloxy,  $C_{1-6}$  alkoxy, phenyl, etc.;  $R^1$  is hydroxy, halo, hydrogen,  $C_{3-8}$  cycloalkyl,  $C_{2-7}$  alkanoyloxy,  $C_{1-6}$  alkoxy, phenyl, etc., or a pharmaceutically acceptable salt, which is useful for the prevention and treatment of physiological disorder associated with an  $\beta$ -amyloid such as Alzheimer's disease and Down's syndrome (WO 95/17095).

4) A compound of the formula:

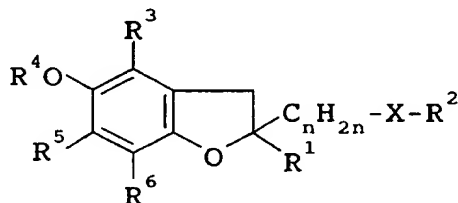
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wherein  $R^1$  is hydrogen or a lower alkyl;  $R^2$  is a methyl substituted by carboxy, alkoxy carbonyl, cyano, halogen, aryl or heterocyclic group, or  $C_{2-15}$  chain-like

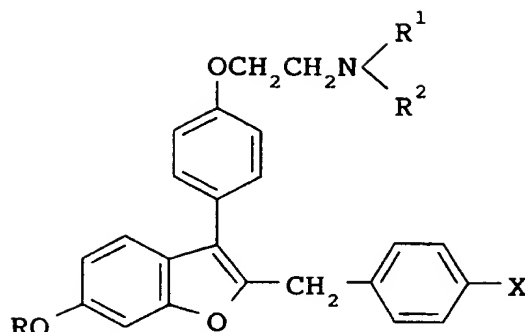
- 5 hydrocarbon residue having no lower alkyl at  $\alpha$ -position which may be substituted by carboxy, alkoxy carbonyl, cyano, halogen, aryl or a heterocyclic group;  $R^3$  is a lower alkyl;  $R^4$  is hydrogen or an acyl;  $R^5$  and  $R^6$  each is a lower alkyl of a lower alkoxy, or  $R^5$  and  $R^6$ , taken together, are butadienylene, or a salt thereof, which has 5- or 12-lipoxygenase inhibiting actions (EP-A-345593, JP-A-2-76869).

5) A compound of the formula:



- 15 wherein  $R^1$  is hydrogen or a lower alkyl;  $n$  is 1 to 6;  $X$  is sulfur which may be oxidized, oxygen or imino which may be substituted;  $R^2$  is methyl or an organic residue bonded through methylene, methylene or quaternary carbon;  $R^3$  is a lower alkyl;  $R^4$  is hydrogen or an acyl;  $R^5$  and  $R^6$  each is a lower alkoxy or a lower alkyl, or  $R^5$  and  $R^6$ , taken together, are butadienylene, or a salt thereof, which has a 5-lipoxygenase inhibiting action (EP-A-345592, JP-A-2-76870).

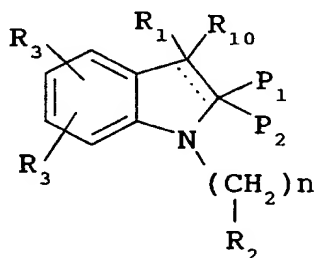
6) A compound of the formula:



wherein R is hydrogen or methyl; R<sup>1</sup> and R<sup>2</sup> each are methyl or ethyl, or R<sup>1</sup> and R<sup>2</sup> taken together are a saturated heterocyclic group; and X is bromo, chloro, fluoro or hydrogen, or a pharmaceutically acceptable salt thereof, which is useful for inhibiting bone loss (EP-A-722726).

Known are the following indole compounds.

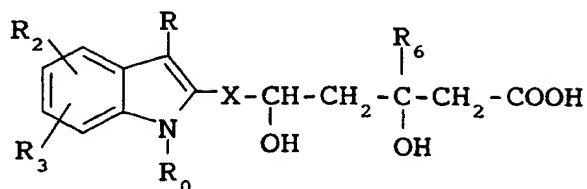
7) A compound of the formula:



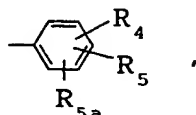
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wherein R<sub>1</sub> is -X(CH<sub>2</sub>)<sub>n</sub>Ar, -X(CH<sub>2</sub>)<sub>n</sub>R<sub>8</sub> etc., R<sub>2</sub> is hydrogen or Ar etc., P<sub>1</sub> is -X(CH<sub>2</sub>)<sub>n</sub>R<sub>8</sub>, P<sub>2</sub> is -X(CH<sub>2</sub>)<sub>n</sub>R<sub>8</sub> etc., R<sub>3</sub> is hydrogen, R<sub>11</sub>, OH, C<sub>1-8</sub> alkoxy, S(O)<sub>q</sub> R<sub>11</sub>, N(R<sub>6</sub>)<sub>2</sub>, Br, F, I, Cl, CF<sub>3</sub>, NHCOR<sub>6</sub>, -R<sub>11</sub>CO<sub>2</sub>R<sub>7</sub>, -XR<sub>9</sub>-Y, XY or -X(CH<sub>2</sub>)<sub>n</sub>R<sub>8</sub>, wherein methylene of the -X(CH<sub>2</sub>)<sub>n</sub>R<sub>8</sub> may be unsubstituted or substituted by one more -(CH<sub>2</sub>)<sub>n</sub>Ar, R<sub>8</sub> is hydrogen, R<sub>11</sub> etc., R<sub>9</sub> is C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, phenyl, etc., R<sub>11</sub> is C<sub>1-8</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, etc., X is (CH<sub>2</sub>)<sub>n</sub>, O, S(O)<sub>q</sub>, Y is CH<sub>3</sub> or -X(CH<sub>2</sub>)<sub>n</sub>Ar, Ar is phenyl, naphthyl, etc., q is 0, 1 or 2, n is an integer of 0 to 6, or a pharmaceutically acceptable salt thereof, which is useful for antagonizing endothelin receptors and treating cerebrovascular diseases (WO 94/14434, JP-A-8-504826).

8) A compound of the formula:



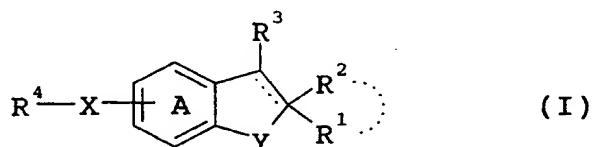
wherein one of R and R<sub>0</sub> is



and the other is C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl or phenyl-(CH<sub>2</sub>)<sub>m</sub>-wherein R<sub>4</sub>, R<sub>5</sub> and R<sub>5a</sub> are hydrogen, etc.; m is 1, 2 or 3; R<sub>2</sub> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-4</sub> alkoxy, phenoxy, benzyloxy, etc.; R<sub>3</sub> is hydrogen, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, phenoxy, benzyloxy, etc.; X is -(CH<sub>2</sub>)<sub>n</sub>- or -CH=CH-; n is 0, 1, 2 or 3; R<sub>6</sub> is hydrogen or C<sub>1-3</sub> alkyl, or a salt thereof, which has cholesterol biosyntheses inhibiting activity (WO 84/02131).

#### DISCLOSURE OF INVENTION

We, the present inventors have studied various compounds and, as a result, have succeeded in the creation of a novel compound of the formula:



wherein R<sup>1</sup> and R<sup>2</sup> each represents a hydrogen atom or a hydrocarbon group which may be substituted, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted; R<sup>3</sup> represents a hydrogen atom, a lower alkyl which may be substituted or an aromatic group which may be substituted; R<sup>4</sup> represents (1) an aromatic group which may be substituted, (2) an aliphatic hydrocarbon group

substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (3) an acyl;

X and Y each represents an oxygen atom or a sulfur atom which may be oxidized;

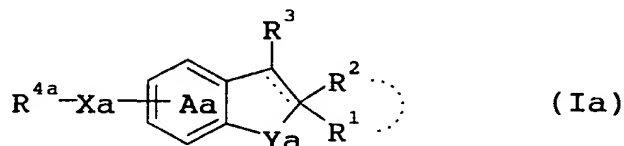
---- represents a single bond or a double bond; and ring A represents a benzene ring which may be further substituted apart from the group of the formula:  $-X-R^4$  wherein each symbol is as defined above,

provided that when X and Y are oxygen atoms and ---- is a single bond,  $R^4$  is not an acyl,

or a salt thereof [hereinafter sometimes referred to briefly as compound (I)], which compound is

structurally characterized in that the benzene ring which is condensed with a 5-membered heterocyclic ring is substituted by a group of the formula:  $-X-R^4$  wherein each symbol is as defined above.

We have found for the first time that compound (I), being based on its specific chemical structure, and a compound of the formula:



wherein  $R^{4a}$  represents an aromatic group which may be substituted, an aliphatic hydrocarbon group which may be substituted or an acyl;

Xa represents an oxygen atom or a sulfur atom which may be oxidized;

Ya represents an oxygen atom, a sulfur atom which may be oxidized or an imino which may be substituted;

---- represents a single bond or a double bond;

ring Aa represents a benzene ring which may be further substituted apart from (i) the group of the formula:

$-Xa-R^{4a}$  wherein each symbol is as defined above, and (ii) an amino which may be substituted,



and the other symbols are defined as above,  
provided that when Xa and Ya are oxygen atoms and  
---- is a single bond, R<sup>4</sup> is not an acyl, or a salt  
thereof [hereinafter sometimes referred to briefly as  
5 compound (Ia)], have an unexpected, excellent  
suppressive effect on neurodegeneration, low toxicity,  
excellent permeability to the brain and are therefore  
satisfactory as medicines for suppressing  
neurodegeneration. Compound (I) is within the scope of  
10 compound (Ia). On the basis of these findings, the  
inventors have completed the present invention.

Specifically, the present invention relates to:

- 1) compound (I);
- 15 2) a compound of the above 1), wherein R<sup>1</sup> and R<sup>2</sup> each  
is (i) a hydrogen atom or  
(ii) a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub>  
cycloalkyl or C<sub>6-14</sub> aryl group which may be substituted  
by 1 to 5 substituents selected from the group  
20 consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy,  
(3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub>  
alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7)  
optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally  
halogenated C<sub>3-6</sub> cycloalkyl, (9) C<sub>6-14</sub> aryl, (10)  
25 optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally  
halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino,  
(14) mono-C<sub>1-6</sub> alkylamino, (15) mono-C<sub>6-14</sub> arylamino, (16)  
di-C<sub>1-6</sub> alkylamino, (17) di-C<sub>6-14</sub> arylamino, (18) acyl  
selected from the group consisting of formyl, carboxy,  
30 carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl,  
C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-  
carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-  
carbonyl, 5- or 6-membered heterocycle carbonyl, mono-  
C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-  
35 carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub>  
alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and  
C<sub>6-14</sub> arylsulfinyl, (19) acylamino selected from the

group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (20) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (22) 5- to 10-membered aromatic heterocyclic group and (23) sulfo, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a C<sub>3-8</sub> cycloalkane or a 3- to 8-membered heterocyclic ring, each of which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl, C<sub>7-16</sub> aralkyl, amino, mono-C<sub>1-6</sub> alkylamino, mono-C<sub>6-14</sub> arylamino, di-C<sub>1-6</sub> alkylamino, di-C<sub>6-14</sub> arylamino and 5- to 10-membered aromatic heterocyclic group;

R<sup>3</sup> is (i) a hydrogen atom, (ii) a C<sub>1-6</sub> alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) C<sub>6-14</sub> aryl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino, (15) mono-C<sub>6-14</sub> arylamino, (16) di-C<sub>1-6</sub> alkylamino, (17) di-C<sub>6-14</sub> arylamino, (18) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub>

alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (19) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (20) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (22) 5- to 10-membered aromatic heterocyclic group and (23) sulfo, or (iii) a C<sub>6-14</sub> aryl or a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-

carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy;

R<sup>4</sup> is (i) a C<sub>6-14</sub> aryl or a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub>

alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy, (ii) an aliphatic hydrocarbon group selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C<sub>3-6</sub> cycloalkyl, which hydrocarbon group substituted by 1 to 3 C<sub>6-14</sub> aryl or 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub>

alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy, which hydrocarbon group may be further substituted by 1 to 5 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) C<sub>6-14</sub> aryl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino, (15) mono-C<sub>6-14</sub> arylamino, (16) di-C<sub>1-6</sub> alkylamino, (17) di-C<sub>6-14</sub> arylamino, (18) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (19) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (20) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy,

(21) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (22) 5- to 10-membered aromatic heterocyclic group and (23) sulfo, or (iii) an acyl of the formula:  $-(C=O)-R^5$ ,  $-(C=O)-OR^5$ ,  $-(C=O)-NR^5R^6$ ,  $-(C=S)-NHR^5$ ,  $-SO_2-R^{5a}$  or  $-SO-R^{5a}$  wherein R<sup>5</sup> is (a) a hydrogen atom, (b) a C<sub>6-14</sub> aryl or a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18)

acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy, or (c) a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl or C<sub>3-6</sub> cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of (1) C<sub>6-14</sub> aryl or 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1') halogen atoms, (2') C<sub>1-3</sub> alkylenedioxy, (3') nitro, (4') cyano, (5') optionally halogenated C<sub>1-6</sub> alkyl, (6') optionally halogenated C<sub>2-6</sub> alkenyl, (7') optionally halogenated C<sub>2-6</sub> alkynyl, (8') optionally halogenated C<sub>3-6</sub> cycloalkyl, (9') optionally halogenated C<sub>1-6</sub> alkoxy, (10') optionally halogenated C<sub>1-6</sub> alkylthio, (11') hydroxy, (12') amino, (13') mono-C<sub>1-6</sub> alkylamino, (14') di-C<sub>1-6</sub> alkylamino, (15') 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16') acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17') acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18')



- acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy,
- 5 (19') sulfo, (20') C<sub>6-14</sub> aryl and (21') C<sub>6-14</sub> aryloxy, (2) halogen atoms, (3) C<sub>1-3</sub> alkylenedioxy, (4) nitro, (5) cyano, (6) optionally halogenated C<sub>1-6</sub> alkyl, (7) optionally halogenated C<sub>2-6</sub> alkenyl, (8) optionally halogenated C<sub>2-6</sub> alkynyl, (9) optionally halogenated C<sub>3-6</sub> cycloalkyl, (10) optionally halogenated C<sub>1-6</sub> alkoxy,
- 10 (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino, (15) di-C<sub>1-6</sub> alkylamino, (16) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents
- 15 selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (17) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub>
- 20 arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (18) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (19)
- 25 acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy and (20) sulfo;
- 30 R<sup>5a</sup> is (a) a C<sub>6-14</sub> aryl or a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur
- 35

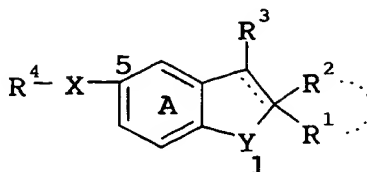
and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy, or (b) a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl or C<sub>3-6</sub> cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of (1) a C<sub>6-14</sub> aryl or 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms

in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1') halogen atoms, (2') C<sub>1-3</sub> alkylenedioxy, (3') nitro, (4') cyano, (5') optionally halogenated C<sub>1-6</sub> alkyl, (6') optionally halogenated C<sub>2-6</sub> alkenyl, (7') optionally halogenated C<sub>2-6</sub> alkynyl, (8') optionally halogenated C<sub>3-6</sub> cycloalkyl, (9') optionally halogenated C<sub>1-6</sub> alkoxy, (10') optionally halogenated C<sub>1-6</sub> alkylthio, (11') hydroxy, (12') amino, (13') mono-C<sub>1-6</sub> alkylamino, (14') di-C<sub>1-6</sub> alkylamino, (15') 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16') acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17') acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18') acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19') sulfo, (20') C<sub>6-14</sub> aryl and (21') C<sub>6-14</sub> aryloxy, (2) halogen atoms, (3) C<sub>1-3</sub> alkylenedioxy, (4) nitro, (5) cyano, (6) optionally halogenated C<sub>1-6</sub> alkyl, (7) optionally halogenated C<sub>2-6</sub> alkenyl, (8) optionally halogenated C<sub>2-6</sub> alkynyl, (9) optionally halogenated C<sub>3-6</sub> cycloalkyl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy,

- (13) amino, (14) mono- $C_{1-6}$  alkylamino, (15) di- $C_{1-6}$  alkylamino, (16) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to 10-membered aromatic heterocyclic group, (17) acyl selected from the group consisting of formyl, carboxy, carbamoyl,  $C_{1-6}$  alkyl-carbonyl,  $C_{3-6}$  cycloalkyl-carbonyl,  $C_{1-6}$  alkoxy-carbonyl,  $C_{6-14}$  aryl-carbonyl,  $C_{7-16}$  aralkyl-carbonyl,  $C_{6-14}$  aryloxy-carbonyl,  $C_{7-16}$  aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono- $C_{1-6}$  alkyl-carbamoyl, di- $C_{1-6}$  alkyl-carbamoyl,  $C_{6-14}$  aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl,  $C_{1-6}$  alkylsulfonyl,  $C_{6-14}$  arylsulfonyl,  $C_{1-6}$  alkylsulfinyl and  $C_{6-14}$  arylsulfinyl, (18) acylamino selected from the group consisting of formylamino,  $C_{1-6}$  alkyl-carboxamido,  $C_{6-14}$  aryl-carboxamido,  $C_{1-6}$  alkoxy-carboxamido,  $C_{1-6}$  alkylsulfonylamino and  $C_{6-14}$  arylsulfonylamino, (19) acyloxy selected from the group consisting of  $C_{1-6}$  alkyl-carbonyloxy,  $C_{6-14}$  aryl-carbonyloxy,  $C_{1-6}$  alkoxy-carbonyloxy, mono- $C_{1-6}$  alkyl-carbamoyloxy, di- $C_{1-6}$  alkyl-carbamoyloxy,  $C_{6-14}$  aryl-carbamoyloxy and nicotinoyloxy and (20) sulfo; and
- $R^6$  is a hydrogen atom or a  $C_{1-6}$  alkyl; and
- ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2)  $C_{1-3}$  alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated  $C_{1-6}$  alkyl, (6) optionally halogenated  $C_{2-6}$  alkenyl, (7) optionally halogenated  $C_{2-6}$  alkynyl, (8) optionally halogenated  $C_{3-6}$  cycloalkyl, (9) optionally halogenated  $C_{1-6}$  alkoxy, (10) optionally halogenated  $C_{1-6}$  alkylthio, (11) hydroxy, (12) amino, (13) mono- $C_{1-6}$  alkylamino, (14) di- $C_{1-6}$  alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to 10-

- membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy.
- 3) a compound of the above 1), wherein R<sup>1</sup> and R<sup>2</sup> each is a C<sub>1-6</sub> alkyl which may be substituted, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted;
- 4) a compound of the above 1), R<sup>3</sup> is an aromatic group which may be substituted;
- 5) a compound of the above 1), wherein R<sup>4</sup> is (i) an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (ii) an acyl;
- 6) a compound of the above 1), wherein X is an oxygen atom;
- 7) a compound of the above 1), wherein Y is an oxygen atom;
- 8) a compound of the above 7), wherein a group of the formula: -X-R<sup>4</sup> is substituted on the 5-position of the benzofuran ring;

9) a compound of the above 1), which is a compound of the formula:



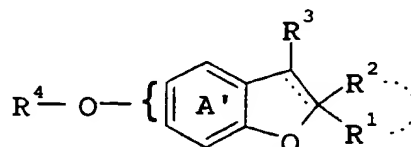
wherein each symbol is as defined above, or a salt thereof;

- 10) a compound of the above 1), wherein  $R^1$  and  $R^2$  each is a  $C_{1-6}$  alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of (1)  $C_{6-14}$  aryl, (2)  $C_{1-6}$  alkoxy, (3)  $C_{1-6}$  alkylthio, (4) hydroxy, (5) amino, (6) mono- $C_{1-6}$  alkylamino, (7) mono- $C_{6-14}$  arylamino, (8) di- $C_{1-6}$  alkylamino, (9) di- $C_{6-14}$  arylamino, (10) carboxy, (11)  $C_{1-6}$  alkylsulfonyl, (12)  $C_{6-14}$  arylsulfonyl, (13)  $C_{1-6}$  alkylsulfinyl, (14)  $C_{6-14}$  arylsulfinyl and (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to 10-membered aromatic group, or  $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl,  $C_{7-16}$  aralkyl and 5- to 10-membered aromatic heterocyclic group;
- $R^3$  is a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2)  $C_{1-6}$  alkyl, (3)  $C_{1-6}$  alkoxy, (4) mono- $C_{1-6}$  alkylamino, (5) di- $C_{1-6}$  alkylamino and (6) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to

10-membered aromatic group;

- $R^4$  is (i)  $C_{1-6}$  alkyl substituted by a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2)  $C_{1-6}$  alkyl, (3)  $C_{1-6}$  alkoxy, (4) hydroxy, (5) amino, (6) mono- $C_{1-6}$  alkylamino, (7) di- $C_{1-6}$  alkylamino, (8) carboxy and (9) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to 10-membered aromatic group, which  $C_{1-6}$  alkyl may be further substituted by carboxy or  $C_{1-6}$  alkoxy-carbonyl, or
- (ii) a  $C_{1-6}$  alkyl-carbonyl,  $C_{3-6}$  cycloalkyl-carbonyl,  $C_{6-14}$  aryl-carbonyl or  $C_{7-16}$  aralkyl-carbonyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, hydroxy, amino, mono- $C_{1-6}$  alkylamino, di- $C_{1-6}$  alkylamino and carboxy;
- X is an oxygen atom;
- Y is an oxygen atom; and
- ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated  $C_{1-6}$  alkyl, optionally halogenated  $C_{1-6}$  alkoxy, amino, mono- $C_{1-6}$  alkylamino and di- $C_{1-6}$  alkylamino;
- 11) a compound of the above 1), wherein  $R^1$  and  $R^2$  each is a  $C_{1-6}$  alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{6-14}$  aryl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkylthio, hydroxy, amino, mono- $C_{1-6}$  alkylamino, mono- $C_{6-14}$  arylamino, di- $C_{1-6}$  alkylamino, di- $C_{6-14}$  arylamino, carboxy,  $C_{1-6}$  alkylsulfonyl,  $C_{6-14}$  arylsulfonyl,  $C_{1-6}$  alkylsulfinyl and  $C_{6-14}$  arylsulfinyl, or

- $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a piperidine which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and  $C_{7-16}$  aralkyl;
- 5  $R^3$  is a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, amino, mono- $C_{1-6}$  alkylamino and di- $C_{1-6}$  alkylamino;
- 10  $R^4$  is (i)  $C_{1-6}$  alkyl substituted by a phenyl or pyridyl, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, hydroxy, amino, mono- $C_{1-6}$  alkylamino, di- $C_{1-6}$  alkylamino and carboxy, or
- 15 (ii) an acyl of the formula:  $-(C=O)-R^{5'}$  wherein  $R^{5'}$  is a phenyl or phenyl- $C_{1-6}$  alkyl, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms,  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, hydroxy, amino, mono- $C_{1-6}$  alkylamino, di- $C_{1-6}$  alkylamino and carboxy;
- 20 X is an oxygen atom;
- Y is an oxygen atom; and
- ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally
- 25 halogenated  $C_{1-6}$  alkyl, optionally halogenated  $C_{1-6}$  alkoxy, amino, mono- $C_{1-6}$  alkylamino and di- $C_{1-6}$  alkylamino;
- 12) a compound of the above 1) which is a compound of the formula:



30 wherein  $R^1$  and  $R^2$  each is  $C_{1-6}$  alkyl which may be substituted by 6-membered saturated cyclic amino substituted by a phenyl, or



$R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a piperidine substituted by a  $C_{1-6}$  alkyl or a  $C_{7-16}$  aralkyl;

$R^3$  is (i) a hydrogen atom, or

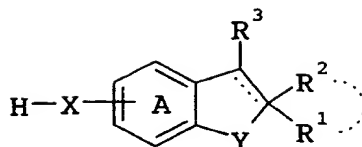
- 5 (ii) a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of (1)  $C_{1-6}$  alkyl, (2) di- $C_{1-6}$  alkylamino and (3) 6-membered saturated cyclic amino which may be substituted by a  $C_{1-6}$  alkyl,

- 10  $R^4$  is (i) a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of nitro and  $C_{1-6}$  alkyl-carboxamido, (ii) a  $C_{1-6}$  alkyl or  $C_{2-6}$  alkenyl group substituted by 1 to 3 of phenyl, quinolyl or pyridyl, each of which may be substituted  
15 by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkoxy-carbonyl,  $C_{1-6}$  alkylsulfonyl and  $C_{1-6}$  alkylsulfinyl, which  $C_{1-6}$  alkyl or  $C_{2-6}$  alkenyl group may be further substituted by a phenyl, carboxy or  $C_{1-6}$  alkoxy-carbonyl,  
20 or

(iii) an acyl of the formula:  $-(C=O)-R^{5'}$

wherein  $R^{5'}$  is phenyl substituted by a  $C_{1-6}$  alkoxy; and ring A' is a benzene ring which may be further substituted by 1 to 3  $C_{1-6}$  alkyl;

- 25 13) a compound of the above 1) which is  
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran,  
3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate,  
30 3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran,  
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine],  
or a salt thereof;  
35 14) a process for producing of compound (I), which comprises reacting a compound of the formula:



wherein each symbol is as defined above, or a salt thereof with a compound of the formula:  $R^4-L$  wherein  $L$  represents a leaving group and  $R^4$  is as defined above, or salt thereof;

15) a pharmaceutical composition which comprises compound (I);

16) a composition of the above 15) which is an agent for suppressing neurodegeneration;

17) a composition of the above 15) which is an agent for suppressing  $\beta$ -amyloid toxicity;

18) a composition of the above 15) which is an agent for preventing and/or treating neurodegenerative diseases;

19) an agent for preventing and/or treating neurodegenerative diseases which comprises compound (Ia);

20) an agent of the above 19) which is an agent for suppressing  $\beta$ -amyloid toxicity;

21) an agent of the above 19) which is an agent for preventing and/or treating neurodegenerative diseases;

22) a method for suppressing neurodegeneration in mammal, which comprises administering to said mammal an effective amount of compound (Ia) with a

pharmaceutically acceptable excipient, carrier or diluent;

23) use of compound (Ia) for manufacturing a pharmaceutical composition for suppressing neurodegeneration; and so forth.

In the formulae, the "hydrocarbon group" of the "hydrocarbon group which may be substituted" for  $R^1$  or  $R^2$  includes, for example, an acyclic or cyclic

hydrocarbon group such as alkyl, alkenyl, alkynyl, cycloalkyl, aryl, etc. Among them, C<sub>1-16</sub> acyclic or cyclic hydrocarbon group is preferable.

5 The preferred "alkyl" is for example C<sub>1-6</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The preferred "alkenyl" is for example C<sub>2-6</sub> alkenyl such as vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, etc.

10 The preferred "alkynyl" is for example C<sub>2-6</sub> alkynyl such as ethynyl, propargyl, butynyl, 1-hexynyl, etc.

The preferred "cycloalkyl" is for example C<sub>3-6</sub> cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

15 The preferred "aryl" is for example C<sub>6-14</sub> aryl such as phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl, etc.

Examples of the "substituents" of the "hydrocarbon group which may be substituted" include halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C<sub>1-3</sub> alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C<sub>1-6</sub> alkyl, optionally halogenated C<sub>2-6</sub> alkenyl, optionally halogenated C<sub>2-6</sub> alkynyl, optionally halogenated C<sub>3-6</sub> cycloalkyl, C<sub>6-14</sub> aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl, etc.), optionally halogenated C<sub>1-6</sub> alkoxy, optionally halogenated C<sub>1-6</sub> alkylthio, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino (e.g., methylamino, ethylamino, etc.), mono-C<sub>6-14</sub> arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), di-C<sub>1-6</sub> alkylamino (e.g., dimethylamino, diethylamino, etc.), di-C<sub>6-14</sub> arylamino (e.g., diphenylamino, etc.), acyl, acylamino, acyloxy, 5- to 7-membered saturated cyclic amino which may be substituted, 5- to 10-membered aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl,

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1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, etc.), sulfo, and so forth.

5 The "hydrocarbon group" may have 1 to 5, preferably 1 to 3 substituents as mentioned above at possible positions of the hydrocarbon group and, when the number of substituents is two or more, those substituents may be the same as or different from one another.

10 The above-mentioned "optionally halogenated C<sub>1-6</sub> alkyl" includes, for example, C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, 15 bromo, iodo, etc.). Concretely mentioned is methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, 20 isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.

The above-mentioned "optionally halogenated C<sub>2-6</sub> alkenyl" includes, for example, C<sub>2-6</sub> alkenyl (e.g., 25 vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, 3,3,3-trifluoro-1-propenyl, 4,4,4-trifluoro-1-butenyl, etc. 30

The above-mentioned "optionally halogenated C<sub>2-6</sub> alkynyl" includes, for example, C<sub>2-6</sub> alkynyl (e.g., ethynyl, propargyl, butynyl, 1-hexynyl, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., 35 fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is ethynyl, propargyl, butynyl, 1-hexynyl, 3,3,3-trifluoro-1-propynyl, 4,4,4-trifluoro-1-butynyl,

etc.

The above-mentioned "optionally halogenated C<sub>3-6</sub> cycloalkyl" includes, for example, C<sub>3-6</sub> cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl, etc.

The above-mentioned "optionally halogenated C<sub>1-6</sub> alkoxy" includes, for example, C<sub>1-6</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.

The above-mentioned "optionally halogenated C<sub>1-6</sub> alkylthio" includes, for example, C<sub>1-6</sub> alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio, etc.

The above-mentioned "acyl" includes, for example, formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, propionyl, etc.), C<sub>3-6</sub> cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), C<sub>1-6</sub> alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C<sub>6-10</sub> aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), C<sub>7-16</sub> aralkyl-

carbonyl (e.g., phenylacetyl, phenylpropionyl, etc.),  
C<sub>6-14</sub> aryloxy-carbonyl (e.g., phenoxycarbonyl, etc.), C<sub>7-16</sub> aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), 5- or 6-membered  
5 heterocycle carbonyl (e.g., nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperidinocarbonyl, 1-pyrrolidinylcarbonyl, etc.),  
mono-C<sub>1-6</sub> alkyl-carbamoyl (e.g., methylcarbamoyl,  
10 ethylcarbamoyl, etc.), di-C<sub>1-6</sub> alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C<sub>6-14</sub> aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), 5- or 6-membered heterocycle  
15 carbamoyl (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), C<sub>1-6</sub> alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), C<sub>6-14</sub> arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.), C<sub>1-6</sub> alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl, etc.), C<sub>6-14</sub> arylsulfinyl (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl, etc.), and so forth.

The above-mentioned "acylamino" includes, for  
25 example, formylamino, C<sub>1-6</sub> alkyl-carboxamido (e.g., acetamido, etc.), C<sub>6-14</sub> aryl-carboxamido (e.g., phenylcarboxamido, naphthylcarboxamido, etc.), C<sub>1-6</sub> alkoxy-carboxamido (e.g., methoxycarboxamido, ethoxycarboxamido, propoxycarboxamido, butoxycarboxamido, etc.), C<sub>1-6</sub> alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), C<sub>6-14</sub> arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino, etc.), and so forth.

35 The above-mentioned "acyloxy" includes, for example, C<sub>1-6</sub> alkyl-carbonyloxy (e.g., acetoxy, propionyloxy, etc.), C<sub>6-14</sub> aryl-carbonyloxy (e.g.,

benzoyloxy, naphthylcarbonyloxy, etc.), C<sub>1-6</sub> alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C<sub>1-6</sub> alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C<sub>1-6</sub> alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C<sub>6-14</sub> aryl-carbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), nicotinoyloxy, and so forth.

10       The above-mentioned "5- to 7-membered saturated cyclic amino" of the "5- to 7-membered saturated cyclic amino which may be substituted" includes, for example, morpholino, thiomorpholino, piperazin-1-yl, piperidino, pyrrolidin-1-yl, etc. The "substituents" of the "5- to  
15       7-membered saturated cyclic amino which may be substituted" include, for example, 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), C<sub>6-14</sub> aryl  
20       (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl, etc.) and 5- to 10-membered aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-  
25       benzo[b]thienyl, benzo[b]furanyl, etc.).

      The "3- to 8-membered carbocyclic ring" of the "3- to 8-membered carbocyclic ring which may be substituted" formed by R<sup>1</sup> and R<sup>2</sup> includes, for example, C<sub>3-8</sub> cycloalkane such as cyclopropane, cyclobutane,  
30       cyclopentane, cyclohexane, etc.

      The "3- to 8-membered heterocyclic ring" of the "3- to 8-membered heterocyclic ring which may be substituted" formed by R<sup>1</sup> and R<sup>2</sup> includes, for example, aziridine, azetidine, morpholine, thiomorpholine,  
35       piperazine, piperidine, pyrrolidine, hexamethyleneimine, heptamethyleneimine, hexahydropyrimidine, etc.

The "substituents" of the "3- to 8-membered carbo or heterocyclic ring which may be substituted" formed by  $R^1$  and  $R^2$  include, for example, 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.),  $C_{6-14}$  aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl, etc.),  $C_{7-16}$  aryl (e.g., benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, etc.), amino, mono- $C_{1-6}$  alkylamino (e.g., methylamino, ethylamino, etc.), mono- $C_{6-14}$  arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), di- $C_{1-6}$  alkylamino (e.g., dimethylamino, diethylamino, etc.), di- $C_{6-14}$  arylamino (e.g., diphenylamino, etc.) and 5- to 10-membered aromatic heterocyclic group (e.g., 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, etc.).

The "lower alkyl" of the "lower alkyl which may be substituted" for  $R^3$  includes, for example,  $C_{1-6}$  alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "substituents" of the "lower alkyl which may be substituted" for  $R^3$  and their number are the same as those mentioned above for the "substituents" of the "hydrocarbon group which may be substituted" for  $R^1$  or  $R^2$ .

The "aromatic group" of the "aromatic group which may be substituted" for  $R^3$  includes, for example, an aromatic hydrocarbon group, an aromatic heterocyclic group, and so forth.

The "aromatic hydrocarbon group" includes, for example, a  $C_{6-14}$  monocyclic or fused polycyclic (e.g., bi- or tri-cyclic) aromatic hydrocarbon group, etc.



Concretely mentioned is C<sub>6-14</sub> aryl such as phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-anthryl, etc.

The "aromatic heterocyclic group" includes, for example, 5- to 14-membered, preferably 5- to 10-membered aromatic heterocyclic group containing one or more (e.g., 1 to 4) hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, etc. Concretely mentioned is a monovalent group formed by removing an optional hydrogen atom from an aromatic heterocyclic ring such as thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, isoindolidine, xanthrene, phenoxathiin, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole,  $\beta$ -carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isoxazole, furazan, phenoxazine, etc.; or a ring as formed through condensation of the above aromatic heterocyclic ring, preferably monocyclic ring, with one or more, preferably one or two aromatic rings (e.g., benzene ring, etc.), etc.

The preferred example of the "aromatic heterocyclic group" is a 5- or 6-membered aromatic heterocyclic group which may be fused with one benzene ring. Concretely mentioned is 2-, 3- or 4-pyridyl, 2-, 3-, 4-, 5- or 8-quinolyl, 1-, 3-, 4- or 5-isoquinolyl, 1-, 2- or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, 2- or 3-thienyl, etc. More preferred is 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-quinolyl, 1-isoquinolyl, 1- or 2-indolyl, 2-benzothiazolyl, etc.

The "substituents" of the "aromatic heterocyclic

group which may be substituted" include, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C<sub>1-3</sub> alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C<sub>1-6</sub> alkyl, 5 optionally halogenated C<sub>2-6</sub> alkenyl, optionally halogenated C<sub>2-6</sub> alkynyl, optionally halogenated C<sub>3-6</sub> cycloalkyl, optionally halogenated C<sub>1-6</sub> alkoxy, optionally halogenated C<sub>1-6</sub> alkylthio, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino (e.g., methylamino, ethylamino, 10 propylamino, isopropylamino, butylamino, etc.), di-C<sub>1-6</sub> alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), 5- to 7-membered saturated cyclic amino which may be substituted, acyl, acylamino, acyloxy, sulfo, C<sub>6-14</sub> aryl 15 (e.g., phenyl, 1-naphthyl, 2-naphthyl, etc.), C<sub>6-14</sub> aryloxy (e.g., phenyloxy, naphthyloxy, etc.), and so forth.

The "aromatic group" may have 1 to 3 substituents as mentioned above at possible positions of the 20 aromatic group and, when the number of substituents is two or more, those substituents may be the same as or different from one another.

The above-mentioned "optionally halogenated C<sub>1-6</sub> alkyl", "optionally halogenated C<sub>2-6</sub> alkenyl", 25 "optionally halogenated C<sub>2-6</sub> alkynyl", "optionally halogenated C<sub>3-6</sub> cycloalkyl", "optionally halogenated C<sub>1-6</sub> alkoxy", "optionally halogenated C<sub>1-6</sub> alkylthio", "5- to 7-membered saturated cyclic amino which may be substituted", "acyl", "acylamino" and "acyloxy" include, 30 for example, those described in detail in the foregoing referring to the "substituents" of the "hydrocarbon group which may be substituted" for R<sup>1</sup> or R<sup>2</sup>, respectively.

35 Preferred example of the "aromatic group which may be substituted" for R<sup>3</sup> is a phenyl, 2-, 3- or 4-pyridyl, 2- or 3-quinolyl or 1-isoquinolyl group, each of which

may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-3</sub> alkylenedioxy, nitro, cyano, optionally halogenated C<sub>1-6</sub> alkyl, optionally halogenated C<sub>2-6</sub> alkenyl, optionally halogenated C<sub>2-6</sub> alkynyl, optionally halogenated C<sub>3-6</sub> cycloalkyl, optionally halogenated C<sub>1-6</sub> alkoxy, optionally halogenated C<sub>1-6</sub> alkylthio, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylamino, 5- to 7-membered saturated cyclic amino which may be substituted, acyl, acylamino, acyloxy, sulfo, C<sub>6-14</sub> aryl and C<sub>6-14</sub> aryloxy.

The "aromatic group which may be substituted" for R<sup>4</sup> includes, for example, 1 to 3, preferably 1 or 2 of the "aromatic group which may be substituted" for R<sup>3</sup> above mentioned.

The "aliphatic hydrocarbon group" of the "aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted" for R<sup>4</sup> includes, for example, alkyl, alkenyl, alkynyl, cycloalkyl, and so forth. Among others, preferred are C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl and C<sub>3-10</sub> cycloalkyl.

The "alkyl" is preferably, for example, C<sub>1-6</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "alkenyl" is preferably, for example, C<sub>2-6</sub> alkenyl such as vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, etc.

The "alkynyl" is preferably, for example, C<sub>2-6</sub> alkynyl such as ethynyl, propargyl, butynyl, 1-hexynyl, etc.

The "cycloalkyl" is preferably, for example, C<sub>3-6</sub> cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

Among others, preferred is C<sub>1-6</sub> alkyl.

The "aromatic group which may be substituted" which the above "aliphatic hydrocarbon group" have,

includes, for example, 1 to 3 of the "aromatic group which may be substituted" for R<sup>3</sup>.

Preferred example of the above "aromatic group which may be substituted" is a phenyl, 2-, 3- or 4-pyridyl, 2- or 3-quinolyl or 1-isoquinolyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-3</sub> alkylenedioxy, nitro, cyano, optionally halogenated C<sub>1-6</sub> alkyl, optionally halogenated C<sub>2-6</sub> alkenyl, optionally halogenated C<sub>2-6</sub> alkynyl, optionally halogenated C<sub>3-6</sub> cycloalkyl, optionally halogenated C<sub>1-6</sub> alkoxy, optionally halogenated C<sub>1-6</sub> alkylthio, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylamino, 5- to 7-membered saturated cyclic amino which may be substituted, acyl, acylamino, acyloxy, sulfo, C<sub>6-14</sub> aryl and C<sub>6-14</sub> aryloxy.

The "substituents" which the above "aliphatic hydrocarbon group" may further have, and their number are the same as those mentioned above for the "substituents" of the "hydrocarbon group which may be substituted" for R<sup>1</sup> or R<sup>2</sup>.

Among them, preferred are acyl such as carboxy, C<sub>1-6</sub> alkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, etc.

The "acyl" for R<sup>4</sup> includes, for example, an acyl of the formula:  $-(C=O)-R^5$ ,  $-(C=O)-OR^5$ ,  $-(C=O)-NR^5R^6$ ,  $-(C=S)-NHR^5$ ,  $-SO_2-R^{5a}$  or  $-SO-R^{5a}$  wherein R<sup>5</sup> is a hydrogen atom, an aromatic group which may be substituted or an aliphatic hydrocarbon group which may be substituted; R<sup>5a</sup> is an aromatic group which may be substituted or an aliphatic hydrocarbon group which may be substituted; and R<sup>6</sup> is a hydrogen atom or C<sub>1-6</sub> alkyl.

The "aromatic group which may be substituted" for R<sup>5</sup> or R<sup>5a</sup> includes, for example, the "aromatic group which may be substituted" for R<sup>3</sup> above.

The "aliphatic hydrocarbon group" of the "aliphatic hydrocarbon group which may be substituted"

for R<sup>5</sup> or R<sup>5a</sup> includes, for example, the "aliphatic hydrocarbon group" of the "aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted" for R<sup>4</sup> above.

The "substituents" of the "aliphatic hydrocarbon group which may be substituted" for R<sup>5</sup> or R<sup>5a</sup> include, for example, (1) the "aromatic group which may be substituted" of the "aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted" for R<sup>4</sup> above, (2) halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), (3) C<sub>1-3</sub> alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), (4) nitro, (5) cyano, (6) optionally halogenated C<sub>1-6</sub> alkyl, (7) optionally halogenated C<sub>2-6</sub> alkenyl, (8) optionally halogenated C<sub>2-6</sub> alkynyl, (9) optionally halogenated C<sub>3-6</sub> cycloalkyl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino (e.g., methylamino, ethylamino, etc.), (15) di-C<sub>1-6</sub> alkylamino (e.g., dimethylamino, diethylamino, etc.), (16) 5- to 7-membered saturated cyclic amino which may be substituted, (17) acyl, (18) acylamino, (19) acyloxy, (20) sulfo, and so forth.

The above-mentioned "optionally halogenated C<sub>1-6</sub> alkyl", "optionally halogenated C<sub>2-6</sub> alkenyl", "optionally halogenated C<sub>2-6</sub> alkynyl", "optionally halogenated C<sub>3-6</sub> cycloalkyl", "optionally halogenated C<sub>1-6</sub> alkoxy", "optionally halogenated C<sub>1-6</sub> alkylthio", "5- to 7-membered saturated cyclic amino which may be substituted", "acyl", "acylamino" and "acyloxy" include, for example, those described in detail in the foregoing referring to the "substituents" of the "hydrocarbon group which may be substituted" for R<sup>1</sup> or R<sup>2</sup>, respectively.

The "aliphatic hydrocarbon group" may have 1 to 5, preferably 1 to 3 substituents as mentioned above at possible positions of the aliphatic hydrocarbon group and, when the number of substituents is two or more, those substituents may be the same as or different from one another.

Preferably,  $R^5$  and  $R^{5a}$  each is an aromatic group which may be substituted.

The " $C_{1-6}$  alkyl" for  $R^6$  includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "sulfur atom which may be oxidized" for X or Y includes S, SO and  $SO_2$ .

The "substituents" which ring A may have apart from the group of the formula:  $-X-R^4$ , include, for example, the "substituents" of the "aromatic group which may be substituted" for  $R^3$  above. Ring A may have 1 to 3 substituents as mentioned above at possible positions of the ring and, when the number of substituents is two or more, those substituents may be the same as or different from one another.

Preferably, the "substituents" which ring A may have apart from the group of the formula:  $-X-R^4$ , include, for example, halogen atoms,  $C_{1-3}$  alkylenedioxy, nitro, cyano, optionally halogenated  $C_{1-6}$  alkyl, optionally halogenated  $C_{2-6}$  alkenyl, optionally halogenated  $C_{2-6}$  alkynyl, optionally halogenated  $C_{3-6}$  cycloalkyl, optionally halogenated  $C_{1-6}$  alkoxy, optionally halogenated  $C_{1-6}$  alkylthio, hydroxy, acyl, acyloxy, sulfo,  $C_{6-14}$  aryl,  $C_{6-14}$  aryloxy, and so forth.

The "aromatic group which may be substituted" and the "acyl" for  $R^{4a}$  include, for example, the "aromatic group which may be substituted" and the "acyl" for  $R^4$ , respectively.

The "aliphatic hydrocarbon group which may be substituted" for  $R^{4a}$  includes, for example, the "aliphatic hydrocarbon group which may be substituted"

for R<sup>5</sup> or R<sup>5a</sup>.

The "sulfur atom which may be oxidized" for Xa or Ya is same as the "sulfur atom which may be oxidized" for X above.

5       The "substituents" of the "imino which may be substituted" for Ya includes, for example, a hydrocarbon group which may be substituted, an acyl, and so forth.

10       The above "hydrocarbon group which may be substituted" includes, for example, the "hydrocarbon group which may be substituted" for R<sup>1</sup> or R<sup>2</sup>.

15       The above "acyl" includes, for example, that described in detail in the foregoing referring to the "substituents" of the "hydrocarbon group which may be substituted" for R<sup>1</sup> or R<sup>2</sup>.

20       The preferred examples of the "imino which may be substituted" for Ya includes imino, C<sub>1-6</sub> alkylimino (e.g., methylimino, ethylimino, etc.), C<sub>6-14</sub> arylimino (e.g., phenylimino, 1-naphthylimino, 2-naphthylimino, etc.), C<sub>7-16</sub> aralkylimino (e.g., benzylimino, etc.), etc.

25       The "substituents" which ring Aa may have apart from the group of the formula: -Xa-R<sup>4a</sup>, include any substituent apart from an amino which may be substituted, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C<sub>1-3</sub> alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C<sub>1-6</sub> alkyl, optionally halogenated C<sub>2-6</sub> alkenyl, optionally halogenated C<sub>2-6</sub> alkynyl, optionally halogenated C<sub>3-6</sub> cycloalkyl, 30 optionally halogenated C<sub>1-6</sub> alkoxy, optionally halogenated C<sub>1-6</sub> alkylthio, hydroxy, acyl, acyloxy, sulfo, and so forth.

35       The above-mentioned "optionally halogenated C<sub>1-6</sub> alkyl", "optionally halogenated C<sub>2-6</sub> alkenyl", "optionally halogenated C<sub>2-6</sub> alkynyl", "optionally halogenated C<sub>3-6</sub> cycloalkyl", "optionally halogenated C<sub>1-6</sub> alkoxy", "optionally halogenated C<sub>1-6</sub> alkylthio",

"acyl" and "acyloxy" include, for example, those described in detail in the foregoing referring to the "substituents" of the "hydrocarbon group which may be substituted" for  $R^1$  or  $R^2$ , respectively.

5 Ring Aa may have 1 to 3 substituents as mentioned above at possible positions of the ring and, when the number of substituents is two or more, those substituents may be the same as or different from one another.

10 In the above formulae, preferably,  $R^1$  and  $R^2$  each is a  $C_{1-6}$  alkyl which may be substituted, or  $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted.

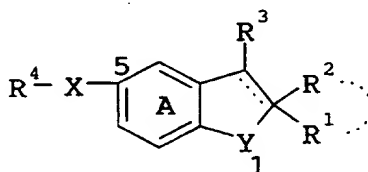
15 Preferably,  $R^3$  is an aromatic group which may be substituted.

20 Preferably,  $R^4$  and  $R^{4a}$  each is (1) an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (2) an acyl.

Preferably, X and Xa each is an oxygen atom.

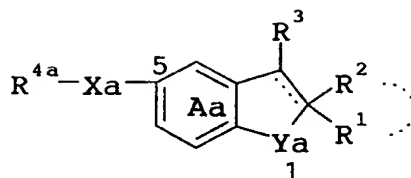
Preferably, Y and Ya each is an oxygen atom.

25 The group of the formula:  $-X-R^4$  is preferably substituted on the 5-position of the basic skeleton as follows.



30 The group of the formula:  $-Xa-R^{4a}$  is preferably substituted on the 5-position of the basic skeleton as follows.





In compound (I), preferred is a compound wherein  $R^1$  and  $R^2$  each is a  $C_{1-6}$  alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of (1)  $C_{6-14}$  aryl, (2)  $C_{1-6}$  alkoxy, (3)  $C_{1-6}$  alkylthio, (4) hydroxy, (5) amino, (6) mono- $C_{1-6}$  alkylamino, (7) mono- $C_{6-14}$  arylamino, (8) di- $C_{1-6}$  alkylamino, (9) di- $C_{6-14}$  arylamino, (10) carboxy, (11)  $C_{1-6}$  alkylsulfonyl, (12)  $C_{6-14}$  arylsulfonyl, (13)  $C_{1-6}$  alkylsulfinyl, (14)  $C_{6-14}$  arylsulfinyl and (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to 10-membered aromatic group, or  $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl,  $C_{7-16}$  aralkyl and 5- to 10-membered aromatic heterocyclic group;

$R^3$  is a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2)  $C_{1-6}$  alkyl, (3)  $C_{1-6}$  alkoxy, (4) mono- $C_{1-6}$  alkylamino, (5) di- $C_{1-6}$  alkylamino and (6) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to 10-membered aromatic group;

$R^4$  is (i)  $C_{1-6}$  alkyl substituted by a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl,

4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-6</sub> alkyl, (3) C<sub>1-6</sub> alkoxy, (4) hydroxy, (5) amino, (6) mono-C<sub>1-6</sub> alkylamino, (7) di-C<sub>1-6</sub> alkylamino, (8) carboxy and (9) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic group, which C<sub>1-6</sub> alkyl may be further substituted by carboxy or C<sub>1-6</sub> alkoxy-carbonyl, or (ii) a C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>6-14</sub> aryl-carbonyl or C<sub>7-16</sub> aralkyl-carbonyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylamino and carboxy; X is an oxygen atom; Y is an oxygen atom; and ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C<sub>1-6</sub> alkyl, optionally halogenated C<sub>1-6</sub> alkoxy, amino, mono-C<sub>1-6</sub> alkylamino and di-C<sub>1-6</sub> alkylamino.

More preferred is a compound wherein R<sup>1</sup> and R<sup>2</sup> each is a C<sub>1-6</sub> alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>6-14</sub> aryl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, mono-C<sub>6-14</sub> arylamino, di-C<sub>1-6</sub> alkylamino, di-C<sub>6-14</sub> arylamino, carboxy, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a piperidine which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub>

alkyl, C<sub>6-14</sub> aryl and C<sub>7-16</sub> aralkyl;

R<sup>3</sup> is a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, amino, mono-C<sub>1-6</sub> alkylamino and di-C<sub>1-6</sub> alkylamino;

R<sup>4</sup> is (i) C<sub>1-6</sub> alkyl substituted by a phenyl or pyridyl, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylamino and carboxy, or

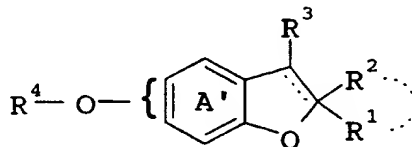
(ii) an acyl of the formula: -(C=O)-R<sup>5'</sup> wherein R<sup>5'</sup> is a phenyl or phenyl-C<sub>1-6</sub> alkyl, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylamino and carboxy;

X is an oxygen atom;

Y is an oxygen atom; and

ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C<sub>1-6</sub> alkyl, optionally halogenated C<sub>1-6</sub> alkoxy, amino, mono-C<sub>1-6</sub> alkylamino and di-C<sub>1-6</sub> alkylamino.

Furthermore the compound of the following formula is also preferred.



wherein R<sup>1</sup> and R<sup>2</sup> each is C<sub>1-6</sub> alkyl which may be substituted by 6-membered saturated cyclic amino substituted by a phenyl, or

R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a piperidine substituted by a C<sub>1-6</sub> alkyl or a C<sub>7-16</sub> aralkyl;

$R^3$  is (i) a hydrogen atom, or  
(ii) a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of (1)  $C_{1-6}$  alkyl, (2) di- $C_{1-6}$  alkylamino and (3) 6-membered saturated cyclic amino which may be substituted by a  $C_{1-6}$  alkyl,  
 $R^4$  is (i) a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of nitro and  $C_{1-6}$  alkyl-carboxamido, (ii) a  $C_{1-6}$  alkyl or  $C_{2-6}$  alkenyl group substituted by 1 to 3 of phenyl, quinolyl or pyridyl, each of which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkoxy-carbonyl,  $C_{1-6}$  alkylsulfonyl and  $C_{1-6}$  alkylsulfinyl, which  $C_{1-6}$  alkyl or  $C_{2-6}$  alkenyl group may be further substituted by a phenyl, carboxy or  $C_{1-6}$  alkoxy-carbonyl, or  
(iii) an acyl of the formula:  $-(C=O)-R^{5'}$   
wherein  $R^{5'}$  is phenyl substituted by a  $C_{1-6}$  alkoxy; and ring A' is a benzene ring which may be further substituted by 1 to 3  $C_{1-6}$  alkyl.

In compound (Ia), preferred is a compound wherein  $R^1$  and  $R^2$  each is a  $C_{1-6}$  alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of (1)  $C_{6-14}$  aryl, (2)  $C_{1-6}$  alkoxy, (3)  $C_{1-6}$  alkylthio, (4) hydroxy, (5) amino, (6) mono- $C_{1-6}$  alkylamino, (7) mono- $C_{6-14}$  arylamino, (8) di- $C_{1-6}$  alkylamino, (9) di- $C_{6-14}$  arylamino, (10) carboxy, (11)  $C_{1-6}$  alkylsulfonyl, (12)  $C_{6-14}$  arylsulfonyl, (13)  $C_{1-6}$  alkylsulfinyl, (14)  $C_{6-14}$  arylsulfinyl and (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to 10-membered aromatic group, or  
 $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring

- which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl, C<sub>7-16</sub> aralkyl and 5- to 10-membered aromatic heterocyclic group;
- 5 R<sup>3</sup> is a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl group, each of which may be substituted by 1 to 3 substituents selected from the group
- 10 consisting of (1) halogen atoms, (2) C<sub>1-6</sub> alkyl, (3) C<sub>1-6</sub> alkoxy, (4) mono-C<sub>1-6</sub> alkylamino, (5) di-C<sub>1-6</sub> alkylamino and (6) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to
- 15 10-membered aromatic group;
- R<sup>4a</sup> is (i) C<sub>1-6</sub> alkyl substituted by a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl group, each of
- 20 which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-6</sub> alkyl, (3) C<sub>1-6</sub> alkoxy, (4) hydroxy, (5) amino, (6) mono-C<sub>1-6</sub> alkylamino, (7) di-C<sub>1-6</sub> alkylamino, (8) carboxy and (9) 5- to 7-membered saturated cyclic amino
- 25 which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic group, which C<sub>1-6</sub> alkyl may be further substituted by carboxy or C<sub>1-6</sub> alkoxy-carbonyl, or
- 30 (ii) a C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>6-14</sub> aryl-carbonyl or C<sub>7-16</sub> aralkyl-carbonyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono-C<sub>1-6</sub>
- 35 alkylamino, di-C<sub>1-6</sub> alkylamino and carboxy;
- Xa is an oxygen atom;

Ya is an oxygen atom; and  
ring Aa is a benzene ring which may be further  
substituted by 1 to 3 substituents selected from the  
group consisting of halogen atoms, optionally  
5 halogenated C<sub>1-6</sub> alkyl and optionally halogenated C<sub>1-6</sub>  
alkoxy.

More preferred is a compound wherein R<sup>1</sup> and R<sup>2</sup> each  
is a C<sub>1-6</sub> alkyl which may be substituted by 1 to 3  
substituents selected from the group consisting of C<sub>6-14</sub>  
10 aryl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, hydroxy, amino, mono-  
C<sub>1-6</sub> alkylamino, mono-C<sub>6-14</sub> arylamino, di-C<sub>1-6</sub> alkylamino,  
di-C<sub>6-14</sub> arylamino, carboxy, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub>  
arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl,  
or

15 R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon  
atom, a piperidine which may be substituted by 1 to 3  
substituents selected from the group consisting of C<sub>1-6</sub>  
alkyl, C<sub>6-14</sub> aryl and C<sub>7-16</sub> aralkyl;

R<sup>3</sup> is a phenyl which may be substituted by 1 to 3  
20 substituents selected from the group consisting of  
halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, amino, mono-C<sub>1-6</sub>  
alkylamino and di-C<sub>1-6</sub> alkylamino;

R<sup>4a</sup> is (i) C<sub>1-6</sub> alkyl substituted by a phenyl or pyridyl,  
each of which may be substituted by 1 to 3 substituents  
25 selected from the group consisting of halogen atoms,  
C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono-C<sub>1-6</sub>  
alkylamino, di-C<sub>1-6</sub> alkylamino and carboxy, or

(ii) an acyl of the formula: -(C=O)-R<sup>5'</sup> wherein R<sup>5'</sup> is  
a phenyl or phenyl-C<sub>1-6</sub> alkyl, each of which may be  
30 substituted by 1 to 3 substituents selected from the  
group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub>  
alkoxy, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub>  
alkylamino and carboxy;

Xa is an oxygen atom;

35 Ya is an oxygen atom; and  
ring Aa is a benzene ring which may be further

substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C<sub>1-6</sub> alkyl and optionally halogenated C<sub>1-6</sub> alkoxy.

5

As compound (I) or (Ia), concretely mentioned are  
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran,  
3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-  
10 yl 4-methoxybenzoate,  
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran,  
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine],  
15 3-(4-isopropylphenyl)-5-(3-pyridylmethyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran,  
and salts thereof.

More Preferred examples are  
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran,  
20 3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate,  
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran,  
25 3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine],  
and salts thereof.

Salts of compound (I) or compound (Ia) include,  
30 for example, metal salts, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids, etc. Preferred examples of metal salts include alkali metal salts such as sodium salts, potassium salts;  
35 alkaline earth metal salts such as calcium salts, magnesium salts, barium salts; aluminium salts, etc. Preferred examples of salts with organic bases include

salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Preferred examples of salts with inorganic acids include hydrochlorides, hydrobromides, nitrates, sulfates, phosphates, etc. Preferred examples of salts with organic acids include formates, acetates, trifluoroacetates, fumarates, oxalates, tartrates, maleates, citrates, succinates, malates, methanesulfonates, benzenesulfonates, p-toluenesulfonates, etc. Preferred examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc. Preferred examples of salts with acidic amino acids include aspartates, glutamates, etc.

Among others, more preferred are pharmaceutically acceptable salts. For example, for compound (I) or (Ia) having an acidic functional group in the molecule, mentioned are their inorganic salts, such as alkali metal salts (e.g., sodium salts, potassium salts, etc.), and alkaline earth metal salts (e.g., calcium salts, magnesium salts, barium salts, etc.), ammonium salts, etc.; and for compound (I) or (Ia) having a basic functional group in the molecule, mentioned are their inorganic salts such as hydrochlorides, sulfates, phosphates, hydrobromides etc., and organic salts such as acetates, maleates, fumarates, succinates, methanesulfonates, p-toluenesulfonates, citrates, tartrates, etc.

Process for producing compound (I) and compound (Ia) is mentioned below.

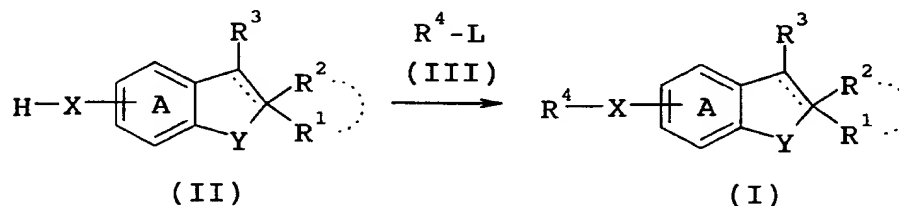
Compound (I) of the present invention can be produced in any per se known manner, for example, according to the methods disclosed in EP-A-273647, JP-A-1-272578, EP-A-483772, JP-A-5-140142, EP-A-345593, JP-A-2-76869, EP-A-345592 and JP-A-2-76870, or



analogous methods thereto, as well as according to the methods of the following process. Compound (Ia) can be produced in the same manner as in the production of compound (I), or in any other *per se* known manner, for example, according to the methods disclosed in WO 94/14434, JP-A-8-504826 and WO 84/02131, or analogous methods thereto.

Each symbol in the compounds in the following process is same as defined above. Compounds (II) and (III) described in the following process include their salts. For their salts, for example, referred to are the same as the salts of compound (I).

#### Process 1



15

Compound (I) is produced by reacting compound (II) with a compound of the formula:  $\text{R}^4\text{-L}$  wherein L represents a leaving group and  $\text{R}^4$  is as defined above [compound (III)].

The "leaving group" for L includes, for example, hydroxy, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), optionally halogenated  $\text{C}_{1-5}$  alkylsulfonyloxy (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, etc.),  $\text{C}_{6-10}$  arylsulfonyloxy which may be substituted. The " $\text{C}_{6-10}$  arylsulfonyloxy which may be substituted" includes, for example,  $\text{C}_{6-10}$  arylsulfonyloxy (e.g. phenylsulfonyloxy, naphthylsulfonyloxy, etc.) which may be substituted by 1 to 3 substituents selected from the group consisting of  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy and nitro. Concretely mentioned is benzenesulfonyloxy, m-

nitrobenzenesulfonyloxy and p-toluenesulfonyloxy, and so forth.

(1) Hereinunder mentioned is the case where R<sup>4</sup> is "an aromatic group which may be substituted" or "an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted".

Compound (II) is reacted with compound (III) optionally in the presence of a base.

The amount of compound (III) to be reacted is from 1.0 to 5.0 mol or so, preferably from 1.0 to 2.0 mol or so, relative to one mol of compound (II).

The "base" includes, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The amount of the base to be used is from 1.0 to 5.0 mol or so, preferably from 1.0 to 2.0 mol or so, relative to one mol of compound (II).

In this reaction, advantageously used is a solvent inert to the reaction. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. For example, preferably used are alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide,

N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc.; and mixtures of those solvents.

The reaction time is generally from 30 minutes to 48 hours, preferably from 1 hour to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from 0 to 150°C.

In place of the reaction mentioned above, also employable herein is Mitsunobu reaction (see Synthesis, pp. 1-27, 1981).

In this reaction, compound (II) is reacted with compound (III) wherein L is OH in the presence of an azodicarboxylate compound (e.g., diethylazo dicarboxylate, etc.) and a phosphine compound (e.g., triphenylphosphine, tributylphosphine, etc.).

The amount of compound (III) wherein L is OH to be reacted is from 1.0 to 5.0 mol or so, preferably from 1.0 to 2.0 mol or so, relative to one mol of compound (II).

The amount of the "azodicarboxylate compound" and that of the "phosphine compound" to be used are from 1.0 to 5.0 mol or so, preferably from 1.0 to 2.0 mol or so, relative to one mol of compound (II), respectively.

In this reaction, advantageously used is a solvent inert to the reaction. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. For example, preferably used are ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon

tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc.; and mixtures of those solvents.

5           The reaction time is generally from 5 minutes to 48 hours, preferably from 30 minutes to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from 0 to 100°C.

10           (2) The case where R<sup>4</sup> is "an acyl" is mentioned below.

Compound (II) is reacted with compound (III) optionally in the presence of a base or acid.

15           The amount of compound (III) to be reacted is from 1.0 to 5.0 mol or so, preferably from 1.0 to 2.0 mol or so, relative to one mol of compound (II).

The "base" includes, for example, aromatic amines such as triethylamine, pyridine, etc.

20           The "acid" includes, for example, methanesulfonic acid, p-toluenesulfonic acid, camphor-sulfonic acid, etc.

The amount of the "base" to be used is from 1.0 to 10 equivalents or so, preferably from 0.8 to 2 equivalents or so, relative to compound (II).

25           The amount of the "acid" to be used is from 0.1 to 10 equivalents or so, preferably from 0.8 to 3 equivalents or so, relative to compound (II).

30           This reaction is advantageously effected in the absence of a solvent or in the presence of a solvent inert to the reaction. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. For example, preferably used are ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.;  
35           hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons

such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc.; nitrogen-containing aromatic hydrocarbons such as pyridine, lutidine, quinoline, etc.; and mixtures of those solvents.

The reaction temperature is generally from -20 to 150°C or so, preferably from 0 to 100°C. The reaction time is generally from 5 minutes to 24 hours, preferably from 10 minutes to 5 hours.

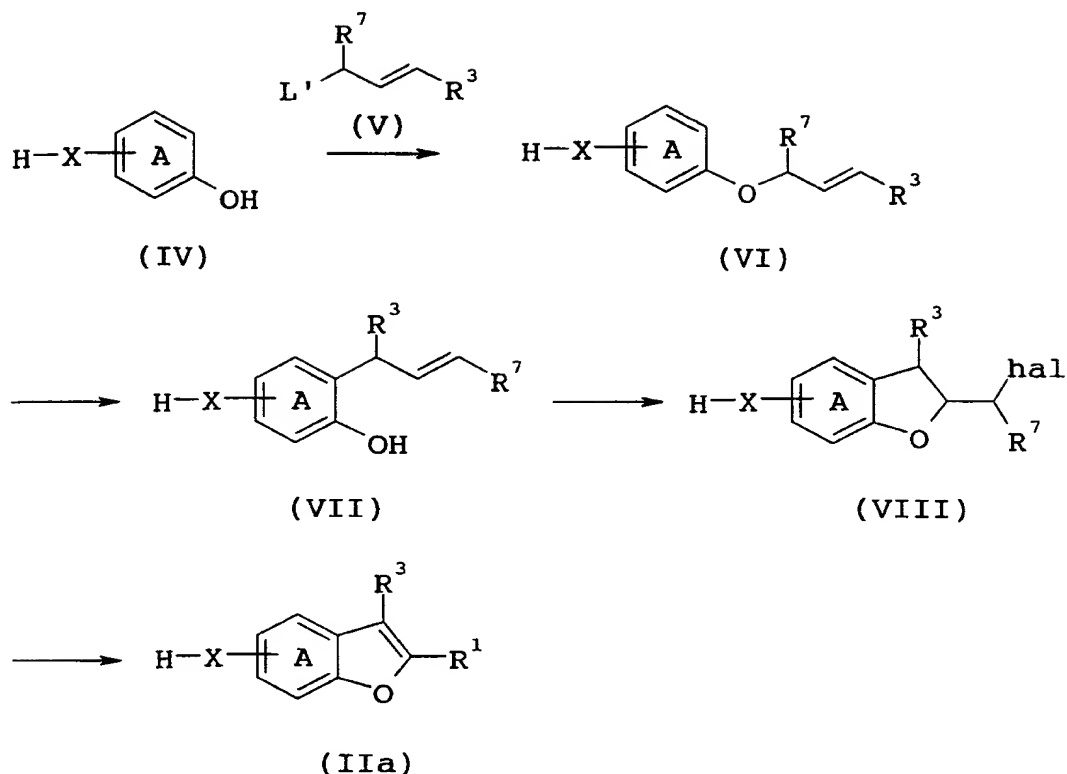
The product (I) as produced in the manner mentioned above may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

Compound (II) can be produced in any *per se* known manner, for example, by the methods disclosed in EP-A-273647, JP-A-1-272578, EP-A-483772, JP-A-5-140142, EP-A-345593, JP-A-2-76869, EP-A-345592, JP-A-2-76870 and JP-A-57-122080, or analogous methods thereto.

Compound (III) can be purchased from a commercial market or produced in any *per se* known manner.

In the case that Compound (II) is a benzofuran [compound (IIa)], it can be also obtained according to the methods of the following process.

## Process 2



In above formulae,  $L'$  represents a leaving group,  $R^7$  represents a hydrogen atom or a group formed by removing a methylene from  $R^1$  and  $hal$  represents halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc).

The "leaving group" for  $L'$  includes, for example, hydroxy, halogen atoms (e.g. fluoro, chloro, bromo, iodo, etc.),  $C_{1-6}$  alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy, etc.),  $C_{6-10}$  arylsulfonyloxy which may be substituted, etc. The " $C_{6-10}$  arylsulfonyloxy which may be substituted" includes, for example,  $C_{6-10}$  arylsulfonyloxy (e.g. phenylsulfonyloxy, naphthylsulfonyloxy, etc.) which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy and nitro. Concretely mentioned is benzenesulfonyloxy, m-nitrobenzenesulfonyloxy, p-toluenesulfonyloxy, and so forth.

Compound (IV) can be purchased from a commercial market or produced in any per se known manner.

Compound (VI) can be produced by reacting a phenolate anion, which is produced by treating compound (IV) with a base, and a compound of the formula:  
5  $R^7\text{-CHL}'\text{-CH=CH-R}^3$  [compound (V)].

The "base" includes, for example, inorganic bases such as alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, etc.; alkali metal  
10 alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; and basic salts  
15 such as potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium acetate, etc. The amount of the base is generally about from 0.5 to 5 mol, preferably about 1 to 3 mol, per mol of compound (IV).

This reaction is advantageously effected in the presence of a solvent inert to the reaction. There is  
20 no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. For example, preferably used are alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as  
25 cyclohexane, hexane, benzene, toluene, xylene, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diethyl ether, diisopropyl ether, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc.;  
30 sulfoxides such as dimethyl sulfoxide etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; ketones such as acetone, methyl ethyl ketone, etc.; water; and mixtures of these solvents.

35 The reaction time is generally from 10 minutes to 8 hours, preferably from 30 minutes to 3 hours. The reaction temperature is generally from 0 to 120°C,

preferably from 25 to 100°C.

The reaction product can be directly used, either as the reaction mixture as such or in a partially purified form, in the next reaction. If desired, however, the product compound can be isolated from the reaction mixture in the routine manner and expediently purified by the conventional purification procedure (e.g. recrystallization, distillation, chromatography, etc.).

Compound (VII) can be produced by subjecting compound (VI) to Claisen rearrangement.

This reaction is advantageously effected in the absence of a solvent or in the presence of a solvent inert to the reaction. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. For example, preferably used are alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as cyclohexane, hexane, benzene, toluene, xylene, mesitylene etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diethyl ether, diisopropyl ether, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc.; sulfoxides such as dimethyl sulfoxide etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; and mixtures of these solvents.

If desired, this reaction can be conducted with acid catalyst.

The "acid catalyst" includes, for example, Lewis acid such as aluminium chloride, boron trifluoride etc. The amount of the acid catalyst is generally from about 0.1 to 20 mol, preferably from about 0.1 to 5 mol, per mol of compound (VI).

The reaction time is generally from 10 minutes to 8 hours, preferably from 30 minutes to 3 hours. The



reaction temperature is from generally -70 to 300°C, preferably from 150 to 250°C.

Thus obtained compound can be submitted to the next reaction either as the reaction mixture or after partial purification, but can be easily isolated by *per se* known method and purified by the routine purification procedures such as recrystallization, distillation, chromatography, etc.

Compound (VIII) can also be produced by treating compound (VII) with a halogenation reagent.

The "halogenation reagent" includes, for example, halogens such as bromine, chlorine, iodine, etc.; imides such as N-bromosuccinimide, etc.; halogen adducts such as benzyltrimethylammonium dichloriodate, benzyltrimethylammonium tribromide, etc.

The amount of the halogenation reagent is from about 1.0 to 5.0 mol, preferably from about 1.0 to 2.0 mol, per mol of compound (VII).

This reaction is advantageously effected in the presence of a solvent inert to the reaction. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. For example, preferably used are ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethyl sulfoxide etc.; organic acids such as acetic acid, propionic acid, etc.; nitroalkanes such as nitromethane, etc.; aromatic amines such as pyridine, lutidine, quinoline, etc.; and mixtures of these solvents.

This reaction can be conducted with a base or a radical initiator, or under light exposure, where necessary.

The "base" includes, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, sodium acetate, potassium acetate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. The amount of the bases is from about 0.8 to 10 mol, per mol of compound (VII).

The "radical initiator" includes, for example, benzoyl peroxide, azobisisobutyronitrile, etc. The amount of the radical initiator is from about 0.01 to 1 mol, per mol of compound (VII).

In the case of the light exposure, halogen lamp can be used.

The reaction temperature is about from -50 to 150°C, preferably from 0 to 100°C. The reaction time is generally from 5 minutes to 24 hours, preferably from 10 minutes to 12 hours.

Thus obtained compound can be submitted to the next reaction either as the reaction mixture or after partial purification, but can be easily isolated by *per se* known method and purified by the routine purification procedures such as recrystallization, distillation, chromatography, etc.

Compound (IIa) can be produced by treating compound (VIII) with a base.

The "base" includes, for example, inorganic bases such as alkali metal hydroxides e.g., sodium hydroxide, potassium hydroxide, etc.; organic bases such as triethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene,

pyridine, etc.; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; basic salts such as potassium hydrogen carbonate, sodium carbonate, potassium carbonate, sodium acetate, etc.

The amount of the base is generally from about 0.5 to 10 mol, preferably about from 1 to 5 mol, per mole of compound (VIII).

This reaction is advantageously effected in the presence of a solvent inert to the reaction. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. For example, preferably used are alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as cyclohexane, hexane, benzene, toluene, xylene, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diethyl ether, diisopropyl ether, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc.; sulfoxides such as dimethyl sulfoxide etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; ketones such as acetone, methyl ethyl ketone, etc.; water; and mixtures of these solvents.

The reaction time is generally from 10 minutes to 24 hours, preferably from 30 minutes to 12 hours. The reaction temperature is generally from 0 to 120°C, preferably from 25 to 100°C.

Thus obtained compound can be submitted to the next reaction either as the reaction mixture or after partial purification, but can be easily isolated by *per se* known method and purified by the routine purification procedures such as recrystallization, distillation, chromatography, etc.

In the above-mentioned reactions where the starting compounds are substituted by any of amino, carboxy or hydroxy, those groups may be protected by ordinary protective groups which are generally used in peptide chemistry. The protective groups may be removed after the reaction to give the intended products.

The amino-protecting group includes, for example, formyl, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, propionyl, etc.) which may be substituted, phenylcarbonyl which may be substituted, C<sub>1-6</sub> alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, etc.) which may be substituted, phenyloxycarbonyl which may be substituted, C<sub>7-10</sub> aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, etc.) which may be substituted, trityl which may be substituted, phthaloyl which may be substituted, etc. These substituents include, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, propionyl, valeryl, etc.), nitro, etc. The number of those substituents is 1 to 3.

The carboxy-protecting group includes, for example, C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.) which may be substituted, phenyl which may be substituted, trityl which may be substituted, silyl which may be substituted, etc. These substituents includes, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), formyl, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, propionyl, butylcarbonyl, etc.), nitro, C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, tert-butyl, etc.), C<sub>6-10</sub> aryl (e.g., phenyl, naphthyl, etc.), etc. The number of those substituents is 1 to 3.

The hydroxy-protecting group includes, for example, C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.) which may be substituted, phenyl which may be substituted, C<sub>7-11</sub> aralkyl (e.g., benzyl, etc.) which may be substituted, formyl which

may be substituted, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, propionyl, etc.) which may be substituted, phenyloxycarbonyl which may be substituted, C<sub>7-11</sub> aralkyl-oxycarbonyl (e.g., benzyloxycarbonyl, etc.) which may be substituted, tetrahydropyranyl which may be substituted, tetrahydrofuranyl which may be substituted, silyl which may be substituted, etc. Those substituents include, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, tert-butyl, etc.), C<sub>7-11</sub> aralkyl (e.g., benzyl, etc.), C<sub>6-10</sub> aryl (e.g., phenyl, naphthyl, etc.), nitro, etc. The number of those substituents is 1 to 4.

Those protective groups may be removed by any per se known methods or analogous methods thereto, such as methods using acids, bases, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc.; and reduction, etc.

The starting compounds for compound (I) include their salts, which are not specifically defined provided that the reaction with those salts gives the intended products. The above salts include, for example, the salts of compound (I) above.

For configurational isomers (E- and Z-forms) of compound (I), they may be isolated and purified through any ordinary separation means of, for example, extraction, recrystallization, distillation, chromatography and the like, to give pure products in any time when the isomers are formed. By the methods described in "Shin Jikken Kagaku Kouza (New Edition of Lectures of Experimental Chemistry)" 14, edited by the Chemical Society of Japan, pp. 251-253, and in Fourth Edition of "Shin Jikken Kagaku Kouza (Lectures of Experimental Chemistry)" 19, edited by the Chemical Society of Japan, pp. 273-274, or analogous methods thereto, the products of compound (I) being produced

are specifically isomerized at the position of the double bond by heating, or with acid catalysts, transition metal catalysts or radical species catalysts, or through exposure to light, or with strong base catalysts or the like, to thereby obtain the intended pure isomers.

Compound (I) includes stereoisomers, depending on the type of the substituents therein, and both single isomers and mixtures of different isomers are within the scope of the present invention.

Compounds (I) and (Ia) may be in any form of their hydrates and non-hydrates.

In any case, products formed in the reaction mixtures may be subjected to deprotection, acylation, alkylation, hydrogenation, oxidation, reduction, chain extension, substituents-exchange reaction and combined reactions thereof, to obtain compound (I).

Where the products are formed in their free form in the reaction, they may be converted into their salts in any ordinary manner. Where they are formed in the form of their salts, they may be converted into free compounds or other salts in any ordinary manner. The thus-obtained compound (I) may be isolated and purified from the reaction mixtures through any ordinary means of, for example, trans-solvation, concentration, solvent extraction, fractionation, crystallization, recrystallization, chromatography and the like.

Where compound (I) exists in the reaction mixtures in the form of its configurational isomers, diastereomers, conformers or the like, they may be optionally isolated into single isomer through the separation and isolation means mentioned above. Where compound (I) is in the form of its racemates, they may be resolved into d- and l-forms through any ordinary optical resolution.

As compound (I) of the present invention and compound (Ia) have an suppressive effect on neurodegeneration, an activity of suppressing nerve cell death to be caused by  $\beta$ -amyloid, and an activity of neurotrophic factors, while having low toxicity and few side effects, they are useful as medicines.

Compound (I) of the present invention and compound (Ia) act on mammals (e.g., mouse, rat, hamster, rabbit, feline, canine, bovine, sheep, monkey, human, etc.) as neurodegeneration inhibitors and neurotrophic factor-like substances, or as  $\beta$ -amyloid toxicity inhibitors, and suppress the nerve cell death in those mammals. In addition, as having an activity of activating cholinergic neurons (e.g., elevation of choline acetyltransferase activity, etc.), compounds (I) and (Ia) increase the acetylcholine content of subjects to which they are administered while activating the function of the central nervous systems of the subjects. Accordingly, compounds (I) and (Ia) are effective for neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's chorea, etc.), peripheral nervous system disorders (e.g., diabetic neuropathy, etc.) and the like, and are used as medicines for preventing and/or treating those diseases and disorders.

As their toxicity is low, compound (I) of the present invention and compound (Ia) are, either directly as they are or after having been formulated into pharmaceutical compositions along with pharmaceutically acceptable carriers in any *per se* known manner, for example, into tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), liquid preparations, injections, suppositories, sustained release preparations, cataplasms, chewing gums, etc., safely administered orally or parenterally (e.g.,

locally, rectally, intravenously, etc.). In the pharmaceutical composition of the present invention, the amount of compound (I) or (Ia) is from 0.01 to 100 % by weight or so of the total weight of the composition. The dose of the composition varies, depending on the subject to which the composition is administered, the administration route employed, the disorder of the subject, etc. For example, for the peroral composition for treating Alzheimer's disease, its dose to adults may be from 0.1 to 20 mg/kg of body weight or so, preferably from 0.2 to 10 mg/kg of body weight or so, more preferably from 0.5 to 10 mg/kg of body weight or so, in terms of the active ingredient of compound (I) or (Ia), and this may be administered once or several times a day. Compounds (I) and (Ia) may be combined with any other active ingredients, for example, cholinesterase inhibitor (e.g., Aricept (donepezil), etc.), brain function activator (e.g., idebenone, vinpocetine, etc.), medicine for Parkinson's disease (e.g., L-dopa, etc.), neurotrophic factors, and so forth. For example, compound (I) or (Ia) is mixed with any of those other active ingredients in any known manner, and formulated into one pharmaceutical composition (for example, in the form of tablets, powders, granules, capsules including soft capsules, liquid preparations, injections, suppositories, sustained-release preparations, etc.); or they may be formulated into separate compositions and administered to the same subject simultaneously or at time intervals.

Any ordinary organic and inorganic carrier substances that are generally used in formulating medicines are usable as the carriers for formulating the pharmaceutical compositions of the present invention. For example, employable are ordinary excipients, lubricants, binders, disintegrators, etc. for formulating solid preparations; and solvents, solubilizers, suspending agents, isotonicizing agents,



buffers, soothing agents, etc. for formulating liquid preparations. If desired, further employable are other additives such as preservatives, antioxidants, colorants, sweeteners, adsorbents, wetting agents, etc.

5       The excipients include, for example, lactose, white sugar, D-mannitol, starch, corn starch, crystalline cellulose, light silicic anhydride, etc.

      The lubricants include, for example, magnesium stearate, calcium stearate, talc, colloidal silica, etc.

10       The binders include, for example, crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methyl cellulose, carboxymethyl cellulose sodium, etc.

15       The disintegrators include, for example, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, carboxymethyl starch sodium, L-hydroxypropyl cellulose, etc.

      The solvents include, for example, water for  
20 injections, alcohol, propylene glycol, macrogol, sesame oil, corn oil, olive oil, etc.

      The solubilizers include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol,  
25 triethanolamine, sodium carbonate, sodium citrate, etc.

      The suspending agents include, for example, surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerin  
30 monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.

35       The isotonizing agents include, for example, glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, etc.

The buffers include, for example, liquid buffers of phosphates, acetates, carbonates, citrates, etc.

The soothing agents include, for example, benzyl alcohol, etc.

5       The preservatives include, for example, parahydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

The antioxidants include, for example, sulfites, ascorbic acid, etc.

10

#### BEST MODE FOR CARRYING OUT THE INVENTION

The invention will be described in more detail hereinunder, with reference to the following Reference Examples, Examples, Formulation Examples and  
15       Experimental Examples, which, however, are to concretely illustrate some embodiments of the invention and are not intended to restrict the scope of the invention. Various changes and modifications can be made within the range that does not deviate the scope  
20       of the invention.

"Room temperature" as referred to in the following Reference Examples and Examples is meant to indicate a temperature falling between 10°C and 35°C. Unless  
25       otherwise specifically indicated, "%" is by weight.

25       The meanings of the abbreviations used hereinunder are as follows:

s: singlet

d: doublet

t: triplet

30       q: quartet

septet : septet

m: multiplet

br: broad

J: coupling constant

35       Hz: Hertz

CDCl<sub>3</sub>: deuterated chloroform

$d_6$ -DMSO: deuterated dimethylsulfoxide

$^1\text{H}$ -NMR: proton nuclear magnetic resonance spectrum

### Examples

#### 5 Reference Example 1

##### Methyl $\alpha$ -bromophenylacetate

Concentrated sulfuric acid (0.5 mL) was added to a solution of  $\alpha$ -bromophenylacetic acid (3.00 g, 13.9 mmol) in ethanol (30 mL) at room temperature, and the mixture was heated under reflux for 1 hour. The reaction mixture was cooled, and extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, then dried over magnesium sulfate, filtered, and concentrated under reduced pressure to obtain the title compound (2.50 g, yield 79 %). This was oily.

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.78 (3H, s), 5.36 (1H, s), 7.29-7.42 (3H, m), 7.48-7.61 (2H, m).

20

#### Reference Example 2

##### 1-Bromo-4-(4-morpholinyl)benzene

Bromine (10.8 g, 67.4 mmol) was added to a solution of 4-(4-morpholinyl)benzene (10.0 g, 61.3 mmol) in ethanol (100 mL) at 0°C, and the mixture was stirred for 1 hour at room temperature. Water (100 mL) was poured into the reaction mixture, which was then extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate and water, then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to obtain the title compound (10.7 g, yield 72 %).

35 m.p.: 118-120°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.98-3.22 (4H, m), 3.71-3.92 (4H, m), 6.72-6.83 (2H, m), 7.31-7.42 (2H, m).

### Reference Example 3

#### 5 1-Bromo-4-(4-methyl-1-piperazinyl)benzene

Sodium hydride (60 % liquid paraffin dispersion, 2.70 g, 67.8 mmol) was added to a solution of 1-phenylpiperazine (10.0 g, 61.6 mmol) in N,N-dimethylformamide (80 mL) at 0°C, and the mixture was stirred for 10 minutes at the same temperature. To the reaction mixture was added iodomethane (8.74 g, 67.8 mmol), and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was poured into water (80 mL), and extracted twice with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from hexane-isopropyl ether to obtain 1-methyl-4-phenylpiperazine (7.40 g). Bromine (7.00 g, 43.8 mmol) was added to a solution of this compound in ethanol (80 mL) at 0°C, and the mixture was stirred for 1 hour at room temperature. Water (80 mL) was poured into the reaction mixture, which was then extracted twice with ethyl acetate. The organic layer was combined, washed with an aqueous saturated sodium hydrogencarbonate and water, then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to obtain the title compound (8.1 g, yield 52 %). m.p.: 78-80°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.35 (3H, s), 2.52-2.63 (4H, m), 3.13-3.26 (4H, m), 6.78 (2H, d,  $J = 8.8$  Hz), 7.33 (2H, d,  $J = 8.8$  Hz).

35

### Reference Example 4

### 2-Methyl-1-[4-(4-morpholinyl)phenyl]propan-1-one

n-Butyllithium (1.6 M, 25.8 mL, 41.3 mmol) was added to a solution of 1-bromo-4-(4-morpholinyl)benzene (10.0 g, 41.3 mmol) in tetrahydrofuran (100 mL) at -78°C, and the mixture was stirred for 20 minutes at the same temperature. To the reaction mixture was added N-isobutyrylpropyleneimine (5.77 g, 45.4 mmol), and the mixture was stirred for 30 minutes at room temperature. Water (40 mL) was poured into the reaction mixture, which was then extracted twice with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from hexane to obtain the title compound (6.50 g, yield 67 %).

m.p.: 75-77°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.19 (6H, d, J = 7.0 Hz), 3.22-3.33 (4H, m), 3.50 (1H, septet, J = 7.0 Hz), 3.81-3.92 (4H, m), 6.81-6.92 (2H, m), 7.85-8.95 (2H, m).

### Reference Example 5

#### 2-Methyl-1-[4-(4-methyl-1-piperazinyl)phenyl]propan-1-one

Using 1-bromo-4-(4-methyl-1-piperazinyl)benzene the title compound was obtained in the same manner as in Reference Example 4.

Yield: 81 %.

m.p.: 74-76°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.19 (6H, d, J = 6.6 Hz), 2.35 (3H, s), 2.46-2.63 (4H, m), 3.32-3.41 (4H, m), 3.50 (1H, septet, J = 7.0 Hz), 6.84-6.92 (2H, m), 7.85-7.95 (2H, m).

### Reference Example 6

1-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-methyl-1-[4-(4-morpholinyl)phenyl]propan-1-ol

n-Butyllithium (1.6 M, 18.1 mL, 29.0 mmol) was added to a solution of 1-bromo-2,5-dimethoxy-3,4,6-trimethylbenzene (7.52 g, 29.0 mmol) in tetrahydrofuran (50 mL) at -78°C, and the mixture was stirred for 20 minutes at the same temperature. To the reaction mixture was added 2-methyl-1-[4-(4-morpholinyl)phenyl]propan-1-one (6.15 g, 26.4 mmol), and the mixture was stirred for 30 minutes at room temperature. Water (40 mL) was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from ethanol to obtain the title compound (8.40 g, yield 90 %).

m.p.: 191-193°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.87-1.10 (6H, m), 2.11 (3H, s), 2.18 (3H, s), 2.45 (3H, s), 2.80-3.18 (8H, m), 3.62 (3H, s), 3.75-3.90 (4H, m), 6.41 (1H, br s), 6.82 (2H, d, J = 8.8 Hz), 7.34 (2H, d, J = 8.8 Hz).

#### Reference Example 7

1-(2,5-Dimethoxy-3,4,6-trimethylphenyl)-2-methyl-1-[4-(4-methyl-1-piperazinyl)phenyl]propan-1-ol

Using 2-methyl-1-[4-(4-methyl-1-piperazinyl)phenyl]propan-1-one, the title compound was obtained in the same manner as in Reference Example 6. Yield: 43 %.

m.p.: 114-116°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.97 (6H, t, J = 6.6 Hz), 2.11 (3H, s), 2.18 (3H, s), 2.34 (3H, s), 2.45 (3H, s), 2.50-2.62 (4H, m), 2.76-3.00 (1H, m), 3.02 (3H, s), 3.10-3.28 (4H, m), 3.62 (3H, s), 6.40 (1H, br s), 6.84 (2H, d, J = 8.8 Hz), 7.33 (2H, d, J = 8.8 Hz).

#### Reference Example 8

3-(4-Isopropylphenyl)-2,2-dimethyl-2,3-dihydrobenzofuran-5-ol

n-Butyllithium (1.6 M, 20.8 mL, 33.2 mmol) was added to a solution of 1-bromo-2,5-dimethoxybenzene (7.2 g, 33.2 mmol) in tetrahydrofuran (20 mL) at -78°C, and the mixture was stirred for 20 minutes at the same temperature. To the reaction mixture was added 1-(4-isopropylphenyl)-2-methylpropan-1-one (5.70 g, 30.0 mmol), and the mixture was stirred for 30 minutes at room temperature. Water (30 mL) was poured into the reaction mixture, which was then extracted three times with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. A mixture of the residue and 48 % hydrobromic acid (30 mL) was heated under reflux for 24 hours in an argon atmosphere. After cooled, water (30 mL) was added to the reaction mixture, which was then extracted twice with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from isopropyl ether-hexane to obtain the title compound (2.1 g, yield 70 %). m.p.: 102-104°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.96 (3H, s), 1.25 (6H, d, J = 7.0 Hz), 1.57 (3H, s), 2.90 (1H, septet, J = 7.0 Hz), 4.28 (1H, s), 4.67 (1H, s), 6.53-6.85 (3H, m), 7.02 (2H, d, J = 8.0 Hz), 7.16 (2H, d, J = 8.0 Hz).

Reference Example 9

2,2,4,6,7-Pentamethyl-3-[4-(4-morpholinyl)phenyl]-2,3-dihydrobenzofuran-5-ol

A mixture of 1-(2,5-dimethoxy-3,4,6-trimethylphenyl)-2-methyl-1-[4-(4-morpholinyl)phenyl]propan-1-ol (8.00 g, 19.3 mmol) and 48 % hydrobromic acid (100 mL) was heated under reflux

for 3 hours in an argon atmosphere. After cooled, an aqueous saturated sodium hydrogencarbonate (30 mL) was added to the reaction mixture, which was then extracted twice with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from isopropyl ether-hexane to obtain the title compound (6.40 g, yield 90 %).

m.p.: 91-93°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (3H, s), 1.46 (3H, s), 1.82 (3H, s), 2.15 (3H, s), 2.17 (3H, s), 2.98-3.24 (4H, m), 3.71-3.99 (4H, m), 4.04 (1H, s), 4.18 (1H, s), 6.44-7.10 (4H, m).

#### Reference Example 10

2,2,4,6,7-Pentamethyl-3-[4-(4-methyl-1-piperazinyl)phenyl]-2,3-dihydrobenzofuran-5-ol

Using 1-(2,5-dimethoxy-3,4,6-trimethylphenyl)-2-methyl-1-[4-(4-methyl-1-piperazinyl)phenyl]propan-1-ol the title compound was obtained in the same manner as in Reference Example 9.

Yield: 55 %.

m.p.: 159-161°C (from ethyl acetate-hexane).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (3H, s), 1.46 (3H, s), 1.81 (3H, s), 2.17 (6H, s), 2.34 (3H, s), 2.48-2.65 (4H, m), 3.08-3.22 (4H, m), 4.03 (1H, s), 6.58-7.20 (4H, m), 1H not confirmed.

#### Reference Example 11

1-(4-Isopropylphenyl)propan-1-ol

Propionyl chloride (11.6 g, 125 mmol) was dropwise added to a suspension of aluminium chloride (16.7 g, 125 mmol) and cumene (18.0 g, 150 mmol) in carbon disulfide (30 mL) at -5°C, and the mixture was stirred for 30 minutes at room temperature. The reaction



5 mixture was poured into water with ice, and the organic layer was separated, washed with an aqueous saturated sodium hydrogencarbonate and water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to obtain 1-(4-isopropylphenyl)propan-1-one (24.7 g). Sodium borohydride (1.29 g, 34.2 mmol) was added to a solution of the thus-obtained compound (13.0 g, 68.4 mmol) in ethanol (80 mL) with cooling with ice, and the mixture was stirred for 30 minutes at 10 room temperature. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to obtain the title compound (11.5 g, 15 yield 79 %). This was oily.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.91 (3H, t, J = 7.4 Hz), 1.25 (6H, d, J = 7.0 Hz), 1.63-1.92 (2H, m), 1.94 (1H, br s), 2.90 (1H, septet, J = 7.0 Hz), 4.47-4.61 (1H, m), 7.16-7.29 (4H, m).

20

#### Reference Example 12

2-[1-(4-Isopropylphenyl)propyl]-3,5,6-trimethyl-1,4-benzoquinone

25 Boron trifluoride/ethyl ether complex (1.30 g, 9.33 mmol) was dropwise added to a suspension of 1-(4-isopropylphenyl)propan-1-ol (5.00 g, 28.0 mmol) and trimethylhydroquinone (4.30 g, 28.0 mmol) in 1,2-dichloroethane (100 mL) at 60°C in a nitrogen atmosphere, and the mixture was stirred for 3 hours at 30 the same temperature. After cooled, the reaction mixture was washed with an aqueous solution of iron(III) chloride and water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel 35 column chromatography (hexane/ethyl acetate = 30/1) to obtain the title compound (5.40 g, yield 62 %).

m.p.: 61-63°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.91 (3H, t, J = 7.4 Hz), 1.22 (6H, d, J = 6.8 Hz), 1.83-2.11 (11H, m), 2.85 (1H, septet, J = 6.8 Hz), 4.02-4.23 (1H, m), 7.02-7.24 (4H, m).

5

#### Reference Example 13

3-(4-Isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-ol

10 A solution of 2-[1-(4-isopropylphenyl)propyl]-3,5,6-trimethyl-1,4-benzoquinone (1.00 g, 0.324 mmol) in ethanol (1.00 liter) was stirred for 5 hours while cooling it with ice-water to keep the solution at room temperature and while exposing it to light from 400 W Bromcinelight Deluxe (manufactured by LPL Co.). The  
15 solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 20/1) to obtain the title compound (0.90 g, yield 90 %). This was oily.  
20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.31 (6H, d, J = 7.0 Hz), 1.98 (3H, s), 2.28 (3H, s), 2.30 (3H, s), 2.43 (3H, s), 2.97 (1H, septet, J = 7.0 Hz), 4.43 (1H, s), 7.26 (4H, s).

#### Reference Example 14

25 2,3,6-Trimethyl-4-[(3-phenyl-2-propenyl)oxy]phenyl acetate

To a solution of 4-hydroxy-2,3,6-trimethylphenyl acetate (10.0 g, 51.5 mmol) in N,N-dimethylformamide (100 mL) was added 1-chloro-3-phenyl-2-propene (7.86 g, 51.5 mmol) and potassium carbonate (7.10 g, 51.5 mmol) and the mixture was stirred under an argon atmosphere  
30 at 60°C for 2 hours. This reaction mixture was poured into water and extracted twice with ethyl acetate. The combined extract was washed with water, dried over magnesium sulfate, and concentrated under reduced  
35 pressure. The residue was crystallized from methanol to obtain the title compound (13.0 g, yield 81%).

m.p.: 104-107° C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.06 (3H, s), 2.13 (3H, s), 2.18 (3H, s), 2.34 (3H, s), 4.66 (2H, dd, J = 5.6, 1.2 Hz), 6.43 (1H, dt, J = 16.2, 5.6 Hz), 5.63 (1H, s), 6.74 (1H, d, J = 16.2 Hz), 7.24-7.46 (5H, m).

#### Reference Example 15

4-Hydroxy-2,3,6-trimethyl-5-(1-phenyl-2-propenyl)phenyl acetate

10        A solution of 2,3,6-trimethyl-4-[(3-phenyl-2-propenyl)oxy]phenyl acetate (10.0 g, 32.2 mmol) in N,N-dimethylaniline (70 mL) was stirred under an argon atmosphere at 200° C for 3 h. After the reaction mixture was cooled, it was diluted with ethyl acetate, 15 washed with 2N hydrochloric acid, and water, and dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to obtain the title compound (7.80 g, yield 78 %).

20        m.p.: 136-138° C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.06 (6H, s), 2.11 (3H, s), 2.33 (3H, s), 4.83-5.18 (2H, m), 5.36 (1H, d, J = 10.0 Hz), 6.32-6.58 (1H, m), 7.18-7.37 (5H, m), 1H not confirmed.

#### 25        Reference Example 16

2,4,6,7-Tetramethyl-3-phenylbenzofuran-5-yl acetate

      To a suspension of 4-hydroxy-2,3,6-trimethyl-5-(1-phenyl-2-propenyl)phenyl acetate (5.10 g, 16.4 mmol) and calcium carbonate (2.13 g, 21.3 mmol) in 30 tetrahydrofuran (20 mL) and methanol (20 mL) was added benzyltrimethylammonium dichloroiodate (6.28 g, 18.0 mmol) slowly. The mixture was stirred at room 35 temperature for 30 minutes. The insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure. To the residue was added ethyl acetate and water. The organic layer was separated and

the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with 10% aqueous sodium hydrogen sulfite, water, an aqueous saturated solution of sodium bicarbonate and brine.

5 The organic layer was dried over magnesium sulfate, treated with activated carbon, filtrated and the filtrate was concentrated in vacuo to provide 5.30 g of 2-iodomethyl-4,6,7-trimethyl-3-phenyl-2,3-dihydrobenzofuran-5-yl acetate. A mixture of this

10 compound (5.30 g, 12.1 mmol) and 1,8-diazabicyclo[5,4,0]-7-undecene (9.0 m, 60.0 mmol) in toluene (20 mL) was stirred under an argon atmosphere at 100°C for 3 hours. To that mixture was added water, and the mixture was extracted with ethyl acetate. The

15 extract was washed with 2N hydrochloric acid, and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1) to obtain the title compound (4.0 g, yield 79 %). This

20 was oily.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.85 (3H, s), 2.15 (3H, s), 2.30 (3H, s), 2.33 (3H, s), 2.44 (3H, s), 7.32-7.48 (5H, m).

#### Reference Example 17

25 2,4,6,7-Tetramethyl-3-phenylbenzofuran-5-ol

To a solution of 2,4,6,7-tetramethyl-3-phenylbenzofuran-5-yl acetate (4.00 g, 13.0 mmol) in a mixture of tetrahydrofuran (32 mL) and methanol (8 mL) was added 8N sodium hydroxide solution (2.0 mL)

30 dropwise and the mixture was stirred at 40°C for 1 hour. The solvent was then distilled off under reduced pressure. To the residue was added 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried over

35 magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from isopropyl

ether-hexane to obtain the title compound (3.0 g, yield 87 %).

m.p.: 102-104°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.96 (3H, s), 2.28 (3H, s), 2.29 (3H, s), 2.44 (3H, s), 4.42 (1H, s), 7.28-7.43 (5H, m).

#### Reference Example 18

1-(2,4-Dimethoxyphenyl)-1-(4-isopropylphenyl)-2-methylpropan-1-ol

Using 1-bromo-2,4-dimethoxybenzene and 1-(4-isopropylphenyl)-2-methylpropan-1-one the title compound was obtained in the same manner as in Reference Example 6. Yield 56 %.

m.p.: 80-81°C (from methanol).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.75 (3H, d, J = 6.6 Hz), 1.08 (3H, d, J = 6.6 Hz), 1.20 (6H, d, J = 7.0 Hz), 2.66 (1H, septet, J = 7.0 Hz), 2.80 (1H, septet, J = 6.6 Hz), 3.48 (3H, s), 3.79 (3H, s), 4.71 (1H, s), 6.39-6.40 (1H, m), 6.50-6.56 (1H, m), 7.04-7.08 (2H, m), 7.19-7.23 (2H, m), 7.40-7.44 (1H, m).

#### Reference Example 19

3-(4-Isopropylphenyl)-2,2-dimethyl-2,3-dihydrobenzofuran-6-ol

A mixture of 1-(2,4-dimethoxyphenyl)-1-(4-isopropylphenyl)-2-methylpropan-1-ol (5.58 g, 17.0 mmol) and 48 % hydrobromic acid (30 mL) was heated under reflux for 24 hours in an argon atmosphere. After the reaction mixture was cooled, an aqueous saturated sodium hydrogencarbonate was added to the mixture, which was then extracted twice with ethyl acetate. The organic layers were combined, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 20/1 to 10/1) to obtain the title

compound (2.43 g, yield 51 %).

m.p.: 114-115°C (from hexane).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (3H, s), 1.24 (6H, d, J = 7.0 Hz),  
1.57 (3H, s), 2.89 (1H, septet, J = 7.0 Hz), 4.25 (1H,  
5 s), 6.15 (1H, br), 6.34-6.38 (2H, m), 6.84-6.88 (1H, m),  
6.99-7.03 (2H, m), 7.13-7.17 (2H, m).

#### Reference Example 20

##### 4-(4-Isopropylbenzoyl)piperidine

10 To 1-acetylisonipecotic acid (41.74 g, 243.8 mmol)  
was added thionyl chloride (200 mL), and the resulting  
mixture was stirred for 30 minutes. The mixture was  
diluted with petroleum ether. The precipitated solid  
was collected and washed with petroleum ether to afford  
15 1-acetylisonipecotoyl chloride. This was added to a  
stirring mixture of cumene (120 mL) and aluminium  
chloride (69.6 g, 522 mmol) and the resulting mixture  
was stirred at 110°C for 1 hour. The mixture was  
poured into ice, and extracted twice with ethyl acetate.  
20 The organic layers were combined, washed with brine,  
dried over magnesium sulfate, filtered, and  
concentrated under reduced pressure. To the residue  
was added concentrated hydrochloric acid (100 mL), and  
the mixture was refluxed for 12 hours. The mixture was  
25 cooled to room temperature and was washed twice with  
diethyl ether. The aqueous solution was made basic  
with 8N sodium hydroxide solution and then extracted  
twice with ethyl acetate. The organic layers were  
combined, washed with an aqueous saturated sodium  
30 hydrogencarbonate, dried over magnesium sulfate,  
filtered, and concentrated under reduced pressure. The  
residue was crystallized from ethyl acetate-hexane to  
obtain the title compound (23.5 g, yield 41 %).  
m.p.: 55-57°C.

35 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.27 (6H, d, J = 6.8 Hz), 1.57-2.70 (5H,  
m), 2.70-2.83 (2H, m), 2.97 (1H, septet, J = 6.8 Hz),

3.16-3.22 (2H, m), 3.34-3.46 (1H, m), 7.30-7.34 (2H, m),  
7.87-7.91 (2H, m).

#### Reference Example 21

##### 5 1-Benzyl-4-(4-isopropylbenzoyl)piperidine

To a solution of 4-(4-isopropylbenzoyl)piperidine  
in N,N-dimethylformamide (100 mL), potassium carbonate  
(9.60 g, 69.5 mmol) and benzyl bromide (8.50 g, 71.5  
mmol) were added, and the resulting mixture was stirred  
10 for 20 hours at room temperature. The mixture was  
poured into water, and extracted twice with ethyl  
acetate. The organic layers were combined, washed with  
an aqueous saturated sodium hydrogencarbonate, dried  
over magnesium sulfate, filtered, and concentrated  
15 under reduced pressure. The residue was crystallized  
from hexane to obtain the title compound (13.53 g,  
yield 66 %).  
m.p.: 76-77°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.26 (6H, d, J = 7.0 Hz), 1.79-1.90 (4H,  
20 m), 2.07-2.20 (2H, m), 2.92-2.99 (3H, m), 3.15-3.30 (1H,  
m), 3.55 (2H, s), 7.24-7.32 (7H, m), 7.85-7.89 (2H, m).

#### Reference Example 22

##### 25 (1-Benzyl-4-piperidyl)(2,5-dimethoxy-3,4,6- trimethylphenyl)(4-isopropylphenyl)methanol

n-Butyllithium (1.6 M, 12.0 mL, 19.2 mmol) was  
added to a solution of 1-bromo-2,5-dimethoxy-3,4,6-  
trimethylbenzene (4.89 g, 18.87 mmol) in  
tetrahydrofuran (100 mL) at -78°C, and the mixture was  
30 stirred for 30 minutes at the same temperature. To the  
reaction mixture was added 1-benzyl-4-(4-  
isopropylbenzoyl)piperidine (5.02 g, 15.6 mmol). The  
mixture was stirred for 30 minutes at the same  
temperature, then poured into the water, and extracted  
35 twice with ethyl acetate. The organic layers were  
combined, washed with an aqueous saturated sodium

hydrogencarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to obtain the title compound (6.54 g, yield 83 %).

5 m.p.: 105-108°C.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.19 (6H, d, J = 6.6 Hz), 1.2-1.5 (2H, m), 1.8-2.0 (4H, m), 2.09 (3H, s), 2.17 (3H, s), 2.39 (3H, s), 2.4-2.5 (1H, m), 2.78-2.88 (3H, m), 2.97 (3H, s), 3.51 (2H, s), 3.60 (3H, s), 6.37 (1H, br), 7.08-  
10 7.12 (2H, m), 7.26-7.34 (7H, m).

#### Reference Example 23

1'-Benzyl-3-(4-isopropylphenyl)-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol

15 To a solution of (1-benzyl-4-piperidyl)(2,5-dimethoxy-3,4,6-trimethylphenyl)(4-isopropylphenyl)methanol (6.41 g, 12.8 mmol) in acetic acid (50 mL) was added 48% hydrobromic acid (60 mL), and the mixture was heated under reflux for 15 hours in  
20 an argon atmosphere. The reaction mixture was cooled to room temperature, made basic with 8N sodium hydroxide solution, and extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, dried  
25 over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to obtain the title compound (4.44 g, yield 76 %).

m.p.: 190-192°C.

30 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.19 (6H, d, J = 7.0 Hz), 1.21-1.41 (2H, m), 1.71-2.00 (5H, m), 2.17 (3H, s), 2.20 (3H, s), 2.27-2.90 (5H, m), 2.97 (3H, s), 3.54 (2H, s), 4.02 (1H, s), 6.6-7.1 (4H, m), 7.20-7.32 (5H, m), 1H not confirmed.

35

#### Reference Example 24



3-(4-Isopropylphenyl)-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol hydrochloride

To a solution of 1'-benzyl-3-(4-isopropylphenyl)-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol (3.51 g, 7.70 mmol) and triethylamine (1.1 mL, 7.9 mmol) in chloroform (40 mL)  $\alpha$ -chloroethyl chloroformate (2.30 g, 16.1 mmol) was added at 0°C. The mixture was refluxed for 1 hour and concentrated under reduced pressure. The residue was refluxed in methanol (20 mL) for 1 hour and concentrated under reduced pressure. The residue was crystallized from ethanol-ethyl acetate to obtain the title compound (2.80 g, yield 90 %). m.p.: >245°C (dec.)

<sup>1</sup>H-NMR(*d*<sub>6</sub>-DMSO)  $\delta$ : 1.18 (6H, d, *J* = 6.6 Hz), 1.34 (2H, br), 1.71 (3H, s), 1.97 (2H, br), 2.08 (3H, s), 2.11 (3H, s), 2.8-3.3 (5H, m), 4.26 (1H, s), 6.6-7.2 (4H, m), 7.53 (1H, s), 8.78 (1H, s), 1H not confirmed.

#### Reference Example 25

3-(4-Isopropylphenyl)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol

A mixture of 3-(4-isopropylphenyl)-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol hydrochloride (2.80 g, 6.97 mmol), formic acid (30 mL) and 37% formalin (30 mL) was stirred for 15 hours at 100°C. The reaction mixture was cooled to room temperature, made basic with 8N sodium hydroxide solution, and extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (Chromatorex NH DM1020, Fuji Silysia Chemical LTD) (hexane/ethyl acetate = 1/1) to obtain the title compound (2.05 g, yield 77 %). m.p.: 114-117°C (from ethyl acetate-hexane).

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.18-1.39 (8H, m), 1.72-2.91 (19H, m), 4.02 (1H, m), 6.6-7.1 (4H, m), 1H not confirmed.

#### Reference Example 26

5 (1-Benzyl-4-piperidyl)(2,5-dimethoxy-3,4,6-trimethylphenyl)methanol

n-Butyllithium (1.6 M, 19.5 mL, 31.2 mmol) was added to a solution of 1-bromo-2,5-dimethoxy-3,4,6-trimethylbenzene (8.00 g, 30.87 mmol) in  
10 tetrahydrofuran (80 mL) at  $-78^\circ\text{C}$ , and the mixture was stirred for 30 minutes at the same temperature. To the reaction mixture was added 1-benzyl-4-formylpiperidine (6.23 g, 30.65 mmol). The mixture was stirred for 30 minutes at room temperature, then poured into water,  
15 and extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column  
20 chromatography (ethyl acetate) to obtain the title compound (6.17 g, yield 52 %). This was oily.

$^1\text{H-NMR}(\text{CDCl}_3)$   $\delta$ : 1.17-2.05 (7H, m), 2.16 (3H, s), 2.17(3H, s), 2.24 (3H, s), 2.79-2.85 (1H, m), 2.98-3.05 (1H, m), 3.48 (2H, s), 3.61 (3H, s), 3.75 (3H, s), 4.59  
25 (1H, m), 7.23-7.32 (5H, m), 1H not confirmed.

#### Reference Example 27

1'-Benzyl-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol

30 To a solution of (1-benzyl-4-piperidyl)(2,5-dimethoxy-3,4,6-trimethylphenyl)methanol (6.10 g, 15.9 mmol) in acetic acid (30 mL) was added 48% hydrobromic acid (40 mL), and the mixture was heated under reflux for 15 hours in an argon atmosphere. The reaction  
35 mixture was cooled to room temperature, made basic with 8N sodium hydroxide solution, and extracted twice with

ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 1/1) to obtain the title compound (4.60 g, yield 86 %). This was amorphous.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.71-2.00 (6H, m), 2.10 (3H, s), 2.11 (3H, s), 2.12 (3H, s), 2.58 (2H, m), 2.87 (2H, s), 3.56 (2H, s), 7.25-7.38 (5H, m), 1H not confirmed.

#### Example 1

5-Benzyloxy-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

Sodium hydride (60 % liquid paraffin dispersion, 68 mg, 1.70 mmol) was added to a solution of 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol (0.5 g, 1.54 mmol) in N,N-dimethylformamide (20 mL) at 0°C, and the mixture was stirred for 10 minutes at the same temperature. To the reaction mixture was added benzyl bromide (290 mg, 1.70 mmol) and the mixture was stirred for further 30 minutes at room temperature. The reaction mixture was poured into water (30 mL), and extracted twice with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from methanol to obtain the title compound (380 mg, yield 60 %).

m.p.: 79-81°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (3H, s), 1.22 (6H, d, J = 6.8 Hz), 1.50 (3H, s), 1.83 (3H, s), 2.16 (3H, s), 2.24 (3H, s), 2.86 (1H, septet, J = 6.8 Hz), 4.09 (1H, s), 4.70 (2H, s), 6.70-7.00 (2H, br), 7.09 (2H, d, J = 8.4 Hz), 7.30-7.50 (5H, m).

## Example 2

5-Benzyloxy-3-[4-(dimethylamino)phenyl]-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

Using 3-[4-(dimethylamino)phenyl]-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and benzyl bromide, the title compound was obtained in the same manner as in Example 1.

Yield: 40 %.

m.p.: 110-112°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.03 (3H, s), 1.48 (3H, s), 1.87 (3H, s), 2.16 (3H, s), 2.23 (3H, s), 2.91 (6H, s), 4.04 (1H, s), 4.70 (2H, s), 6.48-7.16 (4H, m), 7.20-7.48 (5H, m).

## Example 3

5-Benzyloxy-2,4,6,7-tetramethyl-2-(4-phenyl-1-piperazinyl)methyl-2,3-dihydrobenzofuran

Using 2,4,6,7-tetramethyl-2-(4-phenyl-1-piperazinyl)methyl-2,3-dihydrobenzofuran-5-ol and benzyl bromide, the title compound was obtained in the same manner as in Example 1.

Yield: 48 %.

m.p.: 120-121°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 (3H, s), 2.09 (3H, s), 2.16 (3H, s), 2.20 (3H, s), 2.58-2.92 (7H, m), 3.08-3.22 (5H, m), 4.71 (2H, s), 6.78-6.94 (3H, m), 7.20-7.52 (7H, m).

## Example 4

3-(4-Isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and 4-methoxybenzyl chloride, the title compound was obtained in the same manner as in Example 1.

Yield: 49 %.

m.p.: 95-96°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.49 (3H, s), 1.82 (3H, s), 2.16 (3H, s), 2.23 (3H, s), 2.86 (1H, septet, J = 7.0 Hz), 3.81 (3H, s), 4.08 (1H, s), 4.63 (2H, s), 6.70-7.18 (6H, m), 7.35 (2H, d, J = 8.8 Hz).

#### Example 5

3-(4-Isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2-dimethyl-2,3-dihydrobenzofuran

Using (4-isopropylphenyl)-2,2-dimethyl-2,3-dihydrobenzofuran-5-ol and 4-methoxybenzyl chloride, the title compound was obtained in the same manner as in Example 1.

Yield: 75 %.

m.p.: 124-126° C (from ethyl acetate-hexane).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.95 (3H, s), 1.25 (6H, d, J = 7.0 Hz), 1.57 (3H, s), 2.90 (septet, 1H, J = 7.0 Hz), 3.71 (3H, s), 4.30 (1H, s), 4.87 (2H, s), 6.65-7.35 (11H, m).

#### Example 6

3-[4-(Dimethylamino)phenyl]-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

Using 3-[4-(dimethylamino)phenyl]-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and 4-methoxybenzyl chloride, the title compound was obtained in the same manner as in Example 1.

Yield: 42 %.

m.p.: 105-107° C (from ethanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (3H, s), 1.48 (3H, s), 1.84 (3H, s), 2.15 (3H, s), 2.23 (3H, s), 2.92 (6H, s), 3.81 (3H, s), 4.04 (1H, s), 4.58-4.69 (2H, m), 6.54-6.93 (6H, m), 7.30-7.42 (2H, m).

#### Example 7

5-(4-Methoxybenzyloxy)-3-[4-(4-morpholinyl)phenyl]-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

Using 2,2,4,6,7-pentamethyl-3-[4-(4-morpholinyl)phenyl]-2,3-dihydrobenzofuran-5-ol and 4-methoxybenzyl chloride, the title compound was obtained in the same manner as in Example 1.

5 Yield: 38 %.

m.p.: 110-112°C (ethanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (3H, s), 1.48 (3H, s), 1.83 (3H, s), 2.15 (3H, s), 2.23 (3H, s), 3.02-3.26 (4H, m), 3.71-3.99 (7H, m), 4.05 (1H, s), 4.57-4.90 (2H, m),  
10 6.60-7.00 (6H, m), 7.35 (2H, d, J = 6.8 Hz).

#### Example 8

5-(4-Methoxybenzyloxy)-2,2,4,6,7-pentamethyl-3-[4-(4-methyl-1-piperazinyl)phenyl]-2,3-dihydrobenzofuran

15 Using 2,2,4,6,7-pentamethyl-3-[4-(4-methyl-1-piperazinyl)phenyl]-2,3-dihydrobenzofuran-5-ol and 4-methoxybenzyl chloride, the title compound was obtained in the same manner as in Example 1.

Yield: 42 %.

20 m.p.: 121-122°C (from ethyl ether-hexane).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (3H, s), 1.48 (3H, s), 1.83 (3H, s), 2.15 (3H, s), 2.23 (3H, s), 2.34 (3H, s), 2.52-2.63 (4H, m), 3.13-3.24 (4H, m), 3.81 (3H, s), 4.05 (1H, s), 4.58-4.67 (2H, m), 6.60-7.07 (6H, m), 7.35 (2H, d, J =  
25 8.8 Hz).

#### Example 9

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(4-methylthiobenzyloxy)-2,3-dihydrobenzofuran

30 Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and 4-(bromomethyl)phenyl methyl sulfide, the title compound was obtained in the same manner as in Example 1.

Yield: 70 %.

35 m.p.: 118-120°C (from ethanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.49 (3H, s), 1.82 (3H, s), 2.16 (3H, s), 2.22 (3H, s), 2.48 (3H, s), 2.86 (1H, septet, J = 7.0 Hz), 4.08 (1H, s), 4.65 (2H, s), 6.80-7.02 (2H, br), 7.08 (2H, d, J = 8.0 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.36 (2H, d, J = 8.4 Hz).

#### Example 10

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-[4-(methylsulfinyl)benzyloxy]-2,3-dihydrobenzofuran

Sodium periodate (0.766 g, 3.58 mmol) was added to a solution of 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(4-methylthiobenzyloxy)-2,3-dihydrobenzofuran (1.50 g, 3.26 mmol) in a mixture of ethanol (80 mL) and water (8 mol), and the mixture was heated under reflux for 2 hours. To the reaction mixture were added ethyl acetate and water to separate it into two layers, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was recrystallized from ethyl acetate-hexane to obtain the title compound (1.23 g, yield 79 %).

m.p.: 132-134°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (3H, s), 1.22 (6H, d, J = 6.8 Hz), 1.50 (3H, s), 1.82 (3H, s), 2.17 (3H, s), 2.23 (3H, s), 2.71, 2.72 (1.5H x2, s x2), 2.86 (1H, septet, J = 6.8 Hz), 4.09 (1H, s), 4.76 (2H, s), 6.71-7.15 (4H, m), 7.57-7.69 (4H, m).

#### Example 11

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-[4-(methylsulfonyl)benzyloxy]-2,3-dihydrobenzofuran

Sodium periodate (2.02 g, 9.45 mmol) was added to a solution of 3-(4-isopropylphenyl)-2,2,4,6,7-

pentamethyl-5-[(4-methylsulfinyl)benzyloxy]-2,3-dihydrobenzofuran (1.50 g, 3.15 mmol) in a mixture of ethanol (80 mL) and water (8 mol), and the mixture was heated under reflux for 18 hours. To the reaction mixture were added ethyl acetate and water to separate it into two layers, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was recrystallized from ethyl acetate-hexane to obtain the title compound (1.05 g, yield 68 %).

m.p.: 161-162°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.50 (3H, s), 1.82 (3H, s), 2.17 (3H, s), 2.22 (3H, s), 2.87 (1H, septet, J = 7.0 Hz), 3.05 (3H, s), 4.09 (1H, s), 4.80 (2H, s), 6.70-7.13 (4H, m), 7.67 (2H, d, J = 8.4 Hz), 7.95 (2H, d, J = 8.4 Hz).

#### Example 12

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(3-phenyl-2-propen-1-yloxy)-2,3-dihydrobenzofuran

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and 3-bromo-1-phenyl-1-propene, the title compound was obtained in the same manner as in Example 1.

Yield: 71 %.

m.p.: 106-107°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (3H, s), 1.21 (6H, d, J = 7.0 Hz), 1.49 (3H, s), 1.86 (3H, s), 2.16 (3H, s), 2.24 (3H, s), 2.85 (1H, septet, J = 7.0 Hz), 4.08 (1H, s), 4.36 (2H, d, J = 6.0 Hz), 6.42 (1H, dt, J = 15.4, 6.0 Hz), 6.66-7.15 (5H, m), 7.20-7.48 (5H, m).

#### Example 13



3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(2-quinolylmethoxy)-2,3-dihydrobenzofuran hydrochloride

Sodium hydride (60 % liquid paraffin dispersion, 136 mg, 3.39 mmol) was added to a solution of 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol (1.0 g, 3.08 mmol) in N,N-dimethylformamide (30 mL) at 0°C, and the mixture was stirred for 10 minutes at the same temperature. To the reaction mixture was added 2-(chloromethyl)quinoline hydrochloride (730 mg, 3.39 mmol) and the mixture was stirred for 30 minutes at 80°C. The reaction mixture was poured into water (40 mL), and extracted twice with ethyl acetate. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. To the residue was added 4 N HCl-ethanol, and the solvent was removed through distillation. The residue was crystallized from ethanol-hexane to obtain the title compound (1.1 g, yield 71 %).

m.p.: 136-139°C.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.94 (3H, s), 1.18 (6H, d, J = 7.0 Hz), 1.45 (3H, s), 1.78 (3H, s), 2.11 (3H, s), 2.22 (3H, s), 2.85 (1H, septet, J = 7.0 Hz), 4.19 (1H, s), 4.20-4.90 (1H, br), 5.10 (1H, d, J = 15.8 Hz), 5.19 (1H, d, J = 15.8 Hz), 6.65-7.05 (2H, br), 7.13 (2H, d, J = 8.8 Hz), 7.72-7.85 (1H, m), 7.91-8.02 (2H, m), 8.15-8.30 (2H, m), 8.80 (1H, d, J = 8.8 Hz).

#### Example 14

5-(3,3-Diphenylpropyloxy)-3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and 3,3-diphenylpropyl methanesulfonate, the title compound was obtained in the same manner as in Example 1. This was oily.

Yield: 55 %.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.99 (3H, s), 1.21 (6H, d, J = 7.0 Hz), 1.45 (3H, s), 1.71 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 2.48 (1H, d, J = 6.6 Hz), 2.55 (1H, d, J = 6.6 Hz), 2.76-2.93 (1H, m), 3.60 (2H, t, J = 6.6 Hz), 4.07 (1H, s), 4.25 (1H, t, J = 8.0 Hz), 6.60-7.00 (2H, br), 7.06 (2H, d, J = 7.6 Hz), 7.10-7.34 (10H, m).

#### Example 15

Methyl 4-[[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl]oxymethyl]benzoate

Using methyl 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and methyl 4-(bromomethyl)methylbenzoate, the title compound was obtained in the same manner as in Example 1.

Yield: 82 %.

m.p.: 108-110°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.01 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.50 (3H, s), 1.82 (3H, s), 2.16 (3H, s), 2.22 (3H, s), 2.86 (1H, septet, J = 7.0 Hz), 3.92 (3H, s), 4.09 (1H, s), 4.76 (2H, s), 6.65-7.00 (2H, br), 7.08 (2H, d, J = 8.0 Hz), 7.51 (2H, d, J = 8.0 Hz), 8.04 (2H, d, J = 8.2 Hz), 8.07 (1H, s), 4.21-4.37 (4H, m), 6.63-6.98 (2H, br), 7.07 (2H, d, J = 8.0 Hz).

#### Example 16

Methyl α-[[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl]oxy]phenylacetate

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and methyl α-bromophenylacetate, the title compound was obtained in the same manner as in Example 1. This was oily.

Yield: 82 %.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.99 (3H, s), 1.21, 1.23 (6H, each d, J = 7.0 Hz), 1.47 (3H, s), 1.57, 1.60 (3H, each s),

2.00, 2.04 (3H, each s), 2.09, 2.11 (3H, each s), 2.75-2.98 (1H, m), 3.70, 3.74 (3H, each s), 4.01 (1H, s), 5.07 (1H, s), 6.60-6.95 (2H, br), 7.06 (2H, d, J = 8.0 Hz), 7.24-7.50 (5H, m).

5

#### Example 17

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(2-pyridylmethoxy)-2,3-dihydrobenzofuran

10 Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and 2-chloromethylpyridine hydrochloride, the title compound was obtained in the same manner as in Example 1.

Yield: 17 %.

m.p.: 88-89°C (from methanol).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.51 (3H, s), 1.83 (3H, s), 2.17 (3H, s), 2.24 (3H, s), 2.86 (1H, septet, J = 7.0 Hz), 4.10 (1H, s), 4.80 (1H, d, J = 15.8 Hz), 4.89 (1H, d, J = 15.8 Hz), 6.72-7.02 (2H, br), 7.09 (2H, d, J = 8.2 Hz), 7.15-7.25 (1H, m),  
20 7.67-7.81 (2H, m), 8.50-8.58 (1H, m).

#### Example 18

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(3-pyridylmethoxy)-2,3-dihydrobenzofuran

25 Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and 3-chloromethylpyridine hydrochloride, the title compound was obtained in the same manner as in Example 1. This was oily.

Yield: 76 %.

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.50 (3H, s), 1.82 (3H, s), 2.16 (3H, s), 2.22 (3H, s), 2.86 (1H, septet, J = 7.0 Hz), 4.09 (1H, s), 4.73 (2H, s), 6.63-7.02 (2H, br), 7.09 (2H, d, J = 8.2 Hz), 7.24 (1H, dd, J = 7.8, 5.0 Hz), 7.78 (1H, d, J = 7.6 Hz),  
35 8.56 (1H, d, J = 4.0 Hz), 8.60-8.71 (1H, br).

## Example 19

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(4-pyridylmethoxy)-2,3-dihydrobenzofuran

Using 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol and 4-chloromethylpyridine hydrochloride, the title compound was obtained in the same manner as in Example 1. This was oily.

Yield: 52 %.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.02 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.50 (3H, s), 1.82 (3H, s), 2.16 (3H, s), 2.21 (3H, s), 2.78-2.93 (1H, m), 4.08 (1H, s), 4.73 (2H, s), 6.62-7.01 (2H, br), 7.09 (2H, d, J = 8.4 Hz), 7.38 (2H, d, J = 5.8 Hz), 8.60 (2H, d, J = 5.8 Hz).

## Example 20

3-(4-Isopropylphenyl)-5-(2,4-dinitrophenyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran

Sodium hydride (60 % liquid paraffin dispersion, 270 mg, 6.75 mmol) was added to a solution of 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol (2.0 g, 6.16 mmol) in N,N-dimethylformamide (30 mL) at 0°C, and the mixture was stirred for 20 minutes at the same temperature. To the reaction mixture was added 1-chloro-2,4-dinitrobenzene (1.37 g, 6.78 mmol) and the mixture was stirred for 20 minutes at room temperature. The reaction mixture was poured into water (50 mL), and extracted twice with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to obtain the title compound (1.5 g, yield 50 %).

m.p.: 137-139°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (3H, s), 1.22 (6H, d, J = 7.0 Hz), 1.57 (3H, s), 1.66 (3H, s), 2.03 (3H, s), 2.19 (3H, s), 2.86 (1H, septet, J = 7.0 Hz), 4.13 (1H, s), 6.62-6.95

(3H, m), 7.11 (2H, d, J = 8.0 Hz), 8.26 (1H, dd, J = 9.2, 2.6 Hz), 8.75-8.86 (1H, m).

#### Example 21

5 5-(2,4-Bisacetylaminophenyloxy)-3-(4-isopropylphenyl)-  
2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran  
3-(4-Isopropylphenyl)-5-(2,4-dinitrophenyloxy)-  
2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran (800 mg,  
1.63 mmol) and 10 % palladium-carbon (hydrate) (80 mg)  
10 were dispersed in ethanol (40 mL), and the mixture was  
stirred in a hydrogen atmosphere at 60°C for 4 hours.  
The reaction mixture, from which was removed the  
catalyst through filtration, was concentrated under  
reduced pressure to obtain 5-(2,4-diaminophenoxy)-3-(4-  
15 isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-  
dihydrobenzofuran (710 mg). Acetyl chloride (0.26 mL,  
3.63 mmol) was added to a solution of the thus-obtained  
compound (710 mg, 1.65 mmol) and triethylamine (290 mg,  
1.70 mmol) in chloroform (30 mL) at 0°C, and the  
20 mixture was stirred for 1 hour at the same temperature.  
The reaction mixture was poured into water (30 mL), and  
extracted twice with ethyl acetate. The organic layers  
were combined, washed with an aqueous saturated sodium  
hydrogencarbonate, dried over magnesium sulfate,  
25 filtered, and concentrated under reduced pressure. The  
residue was subjected to silica gel column  
chromatography (hexane/ethyl acetate = 1/5) to obtain  
the title compound (640 mg, yield 76 %). This was  
amorphous.

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (3H, s), 1.22 (6H, d, J = 6.8 Hz),  
1.52 (3H, s), 1.64 (3H, s), 2.00 (3H, s), 2.12 (3H, s),  
2.18 (3H, s), 2.23 (3H, s), 2.86 (1H, septet, J = 6.8  
Hz), 4.11 (1H, s), 6.30 (1H, d, J = 9.2 Hz), 6.60-7.03  
(2H, br), 7.05 (2H, d, J = 8.4 Hz), 7.54 (1H, dd, J =  
35 9.2, 2.6 Hz), 7.69 (1H, br s), 8.02 (1H, s), 8.21 (1H,  
d, J = 2.6 Hz).

## Example 22

$\alpha$ -[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yloxy]phenylacetic acid

5           An aqueous solution of 2 N sodium hydroxide (2.5 mL) was dropwise added to a solution of methyl  $\alpha$ -[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yloxy]phenylacetate (1.20 g, 2.54 mmol) in a mixture of tetrahydrofuran (24 mL) and  
10           methanol (6 mL), and the mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, to which was added 2 N hydrochloric acid. Then, this was extracted twice  
15           with ethyl acetate. The organic layers were washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was recrystallized from hexane to obtain the title compound (0.31 g, yield 27 %), which was a mixture of diastereomers (ratio: 8/1).  
20           m.p.: 163-166°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.98 (3H, s), 1.12-1.25 (6H, m), 1.41-1.56 (6H, m), 1.92-2.10 (6H, m), 2.87 (1H, septet,  $J = 6.6$  Hz), 3.99 (1H, s), 5.08-5.10 (1H, m), 5.20-6.00 (1H, br), 6.60-7.17 (4H, m), 7.20-7.39 (5H, m).

25

## Example 23

$\alpha$ -[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yloxy]phenylacetic acid

30           The filtrate in Example 22 was concentrated under reduced pressure to obtain the title compound (0.50 g, yield 43 %), which was amorphous and was a mixture of diastereomers (ratio: 1/3).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.98 (3H, s), 1.16-1.26 (6H, m), 1.39-1.56 (6H, m), 1.91- 2.10 (6H, m), 2.84 (1H, septet,  $J =$

6.8 Hz), 4.00 (1H, m), 5.07-5.10 (1H, s), 5.40-6.30 (1H, br), 6.50-7.14 (4H, m), 7.20-7.40 (5H, m).

#### Example 24

5 3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(3-phenyl-1-propyl)oxy-2,3-dihydrobenzofuran

3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(3-phenyl-2-propen-1-yl)oxy-2,3-dihydrobenzofuran (800 mg, 1.82 mmol) and 10 % palladium-carbon (hydrate) (80 mg) were suspended in ethanol (20 mL), and the mixture was stirred for 3 hours in a hydrogen atmosphere at room temperature. The catalyst was removed through filtration, and the filtrate was concentrated under reduced pressure. The residue was crystallized from methanol to obtain the title compound (610 mg, yield 76 %).

m.p.: 78-80°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.99 (3H, s), 1.22 (6H, d, J = 6.8 Hz), 1.48 (3H, s), 1.81 (3H, s), 2.02-2.22 (8H, m), 2.76-2.91 (3H, m), 3.68 (2H, t, J = 6.4 Hz), 4.07 (1H, s), 6.70-6.92 (2H, br), 7.07 (2H, d, J = 8.8 Hz), 7.15-7.32 (5H, m).

#### Example 25

25 3-(4-Isopropylphenyl)-2,2,4,6,7-pentamethyl-5-(2-phenylethyl)oxy-2,3-dihydrobenzofuran

A solution of 3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ol (1.0 g, 3.08 mmol), 2-phenylethanol (414 mg, 3.39 mmol), triphenylphosphine (890 mg, 3.39 mmol) and diethyl azodicarboxylate (590 mg, 3.39 mmol) in tetrahydrofuran (20 mL) was stirred for 30 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 100/1) to obtain the title compound (150 mg, yield 11 %).

m.p.: 72-74°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.98 (3H, s), 1.21 (6H, d, J = 7.0 Hz), 1.46 (3H, s), 1.72 (3H, s), 2.10 (3H, s), 2.12 (3H, s), 2.83 (1H, septet, J = 7.0 Hz), 3.05 (2H, t, J = 7.0 Hz), 3.85 (2H, t, J = 7.0 Hz), 4.03 (1H, s), 6.65-7.00 (2H, br), 7.06 (2H, d, J = 8.0 Hz), 7.15-7.50 (5H, m).

#### Example 26

3-(4-Isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate

Triethylamine (0.45 mL, 3.21 mmol) was added to a solution of 3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-ol (0.90 g, 2.92 mmol) and 4-methoxybenzoyl chloride (0.55 g, 3.21 mmol) in chloroform (15 mL) at room temperature, and the mixture was stirred for 3 hours at 60°C. Water (30 mL) was poured into the reaction mixture, which was then extracted twice with ethyl acetate. The organic layers were combined, washed with 1 N hydrochloric acid and saturated sodium hydroxide, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was crystallized from ethanol to obtain the title compound (0.52 g, yield 79 %).

m.p.: 113-115°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.28 (6H, d, J = 6.8 Hz), 1.90 (3H, s), 2.18 (3H, s), 2.33 (3H, s), 2.46 (3H, s), 2.95 (1H, septet, J = 6.8 Hz), 3.89 (3H, s), 6.99 (2H, d, J = 9.0 Hz), 7.25 (4H, s), 8.20 (2H, d, J = 8.8 Hz).

#### Example 27

3-(4-Isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran

Using 3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-ol and 4-methoxybenzyl chloride, the title compound was obtained in the same manner as in Example 1. This was oily.



Yield: 64 %.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.31 (6H, d, J = 6.8 Hz), 2.06 (3H, s),  
2.31 (3H, s), 2.34 (3H, s), 2.43 (3H, s), 2.97 (1H,  
septet, J = 6.8 Hz), 3.82 (3H, s), 4.66 (2H, s), 6.91  
5 (2H, d, J = 8.8 Hz), 7.26 (4H, s), 7.40 (2H, d, J = 8.8  
Hz).

#### Example 28

2,4,6,7-Tetramethyl-3-phenylbenzofuran-5-yl 4-  
10 methoxybenzoate

Using 2,4,6,7-tetramethyl-3-phenylbenzofuran-5-ol  
and 4-methoxybenzoyl chloride, the title compound was  
obtained in the same manner as in Example 26.

Yield 64%.

15 m.p.: 152-154°C (from methanol).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.88 (3H, s), 2.18 (3H, s), 2.32 (3H,  
s), 2.46 (3H, s), 3.89 (3H, s), 6.99 (2H, d, J = 9.2  
Hz), 7.29-7.43 (5H, m), 8.20 (2H, d, J = 9.2 Hz).

#### 20 Examples 29

3-(4-Isopropylphenyl)-6-(4-methoxybenzyloxy)-2,2-  
dimethyl-2,3-dihydrobenzofuran

Sodium hydride (60 % liquid paraffin dispersion,  
179.0 mg, 4.48 mmol) was added to a solution of 3-(4-  
25 isopropylphenyl)-2,2-dimethyl-2,3-dihydrobenzofuran-6-  
ol (1.12 g, 4.00 mmol) in N,N-dimethylformamide (15 mL)  
at 0°C, and the mixture was stirred for 30 minutes at  
the same temperature. To the reaction mixture was  
added 4-methoxybenzyl chloride (636.8 mg, 4.07 mmol)  
30 and the mixture was stirred for further 30 minutes at  
room temperature. The reaction mixture was poured into  
water, and extracted twice with ethyl acetate. The  
organic layers were combined, washed with an aqueous  
saturated sodium hydrogencarbonate, dried over  
35 magnesium sulfate, filtered, and concentrated under  
reduced pressure. The residue was subjected to silica

gel column chromatography (hexane/ethyl acetate = 5/1) to obtain the title compound (1.19 g, yield 74 %).

m.p.: 86-88°C (from hexane).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 0.95 (3H, s), 1.24 (6H, d, J = 7.0 Hz), 1.58 (3H, s), 2.89 (1H, septet, J = 7.0 Hz), 3.82 (3H, s), 4.27 (1H, s), 4.96 (2H, s), 6.47-6.52 (2H, m), 6.90-6.95 (3H, m), 7.02 (2H, d, J = 8.1 Hz), 7.16 (2H, d, J = 8.1 Hz), 7.37 (2H, d, J = 8.8 Hz).

#### Example 30

1'-Benzyl-3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]

Sodium hydride (60 % liquid paraffin dispersion, 81.4 mg, 1.81 mmol) was added to a solution of 1'-

benzyl-3-(4-isopropylphenyl)-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol (824.0 mg, 1.81 mmol) in N,N-dimethylformamide (15 mL)

at 0°C, and the mixture was stirred for 30 minutes at the same temperature. To the reaction mixture was

added 4-methoxybenzyl chloride (319.9 mg, 2.04 mmol) and the mixture was stirred for further 30 minutes at room temperature. The reaction mixture was poured into water, and extracted twice with ethyl acetate. The

organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, dried over

magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 3/1) to obtain the title compound (539 mg, yield 52 %).

This was amorphous.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.20 (6H, d, J = 6.8 Hz), 1.27-1.39 (2H, m), 1.81 (3H, s), 1.86-1.96 (2H, m), 2.19 (3H, s), 2.23 (3H, s), 2.35-2.87 (5H, m), 3.52 (2H, s), 3.80 (3H, s), 4.04 (1H, s), 4.62 (2H, s), 6.6-6.9 (4H, m), 7.04-7.08 (2H, m), 7.22-7.36 (7H, m).

## Example 31

1'-Benzyl-5-(4-methoxybenzyloxy)-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]

Sodium hydride (60 % liquid paraffin dispersion, 134.6 mg, 3.37 mmol) was added to a solution of 1'-benzyl-4,6,7-trimethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol (1.01 g, 2.98 mmol) in N,N-dimethylformamide (15 mL) at 0°C, and the mixture was stirred for 30 minutes at the same temperature. To the reaction mixture was added 4-methoxybenzyl chloride (584.9 mg, 3.43 mmol) and the mixture was stirred for further 30 minutes at room temperature. The reaction mixture was poured into water, and extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain the title compound (1.15 g, yield 85 %).  
m.p.: 85-86°C (from hexane).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.80-2.00 (4H, m), 2.10 (3H, s), 2.15 (3H, s), 2.18 (3H, s), 2.60 (4H, br), 2.87 (2H, s), 3.58 (2H, s), 3.83 (3H, s), 4.62 (2H, s), 6.90-6.95 (2H, m), 7.30-7.43 (7H, m).

## Example 32

3-(4-Isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine]

Sodium hydride (60 % liquid paraffin dispersion, 64.3 mmol, 1.61 mmol) was added to a solution of 3-(4-isopropylphenyl)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol (509.0 mg, 1.34 mmol) in N,N-dimethylformamide (25 mL) at 0°C, and the mixture was stirred for 30 minutes at the same temperature. To the reaction mixture was added 4-methoxybenzyl chloride

(244.0 mg, 1.56 mmol) and the mixture was stirred for further 30 minutes at room temperature. The reaction mixture was poured into water, and extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (Chromatorex NH DM1020, Fuji Silysia Chemical LTD) (hexane/ethyl acetate = 1/1) to obtain the title compound (262 mg, yield 39 %). This was amorphous.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.21 (6H, d, J = 7.0 Hz), 1.3-1.4 (2H, m), 1.82 (3H, s), 1.99-2.04 (2H, m), 2.19 (3H, s), 2.23 (3H, s), 2.30 (3H, s), 2.37-2.70 (4H, m), 2.82 (1H, septet, J = 7.0 Hz), 3.81 (3H, s), 4.05 (1H, s), 4.62 (2H, s), 6.6-6.9 (4H, m), 7.05-7.09 (2H, m), 7.33-7.37 (2H, m).

### Example 33

3-(4-Isopropylphenyl)-1',4,6,7-tetramethyl-5-(4-pyridylmethoxy)spiro[benzofuran-2(3H),4'-piperidine]

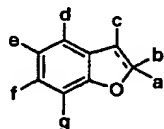
Sodium hydride (60 % liquid paraffin dispersion, 187.3 mg, 4.98 mmol) was added to a solution of 3-(4-isopropylphenyl)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine]-5-ol (817.7 mg, 2.15 mmol) in N,N-dimethylformamide (30 mL) at 0°C, and the mixture was stirred for 30 minutes at the same temperature. To the reaction mixture was added 4-chloromethylpyridine hydrochloride (364.5 mg, 2.22 mmol) and the mixture was stirred for further 30 minutes at room temperature. The reaction mixture was poured into water, and extracted twice with ethyl acetate. The organic layers were combined, washed with an aqueous saturated sodium hydrogencarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column

chromatography (Chromatorex NH DM1020, Fuji Silysia Chemical LTD) (hexane/ethyl acetate = 4/1) to obtain the title compound (575 mg, yield 57 %).  
m.p.: 96-98° C (from hexane).

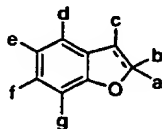
- 5 <sup>1</sup>H-NMR(CDCl<sub>3</sub>) δ: 1.21 (6H, d, J = 7.0 Hz), 1.34-1.41 (2H, m), 1.82 (3H, s), 1.92-2.11 (2H, m), 2.19 (3H, s), 2.21 (3H, s), 2.30 (3H, s), 2.37-2.65 (4H, m), 2.85 (1H, septet, J = 7.0 Hz), 4.05 (1H, s), 4.72 (2H, s), 6.6-7.1 (4H, m), 7.36-7.39 (2H, m), 8.58-8.61 (2H, m).

10

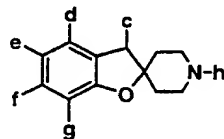
The chemical structural formulae of the compounds obtained in these Examples are shown below.



Ex. No.	a	b	c	d	e	f	g	==
1	Me	Me		Me		Me	Me	—
2	Me	Me		Me		Me	Me	—
3	Me		H	Me		Me	Me	—
4	Me	Me		Me		Me	Me	—
5	Me	Me		H		H	H	—
6	Me	Me		Me		Me	Me	—
7	Me	Me		Me		Me	Me	—
8	Me	Me		Me		Me	Me	—
9	Me	Me		Me		Me	Me	—
10	Me	Me		Me		Me	Me	—
11	Me	Me		Me		Me	Me	—
12	Me	Me		Me		Me	Me	—
13	Me	Me		Me		Me	Me	—
14	Me	Me		Me		Me	Me	—



Ex. No.	a	b	c	d	e	f	g	=
15	Me	Me		Me		Me	Me	—
16	Me	Me		Me		Me	Me	—
17	Me	Me		Me		Me	Me	—
18	Me	Me		Me		Me	Me	—
19	Me	Me		Me		Me	Me	—
20	Me	Me		Me		Me	Me	—
21	Me	Me		Me		Me	Me	—
22	Me	Me		Me		Me	Me	—
23	Me	Me		Me		Me	Me	—
24	Me	Me		Me		Me	Me	—
25	Me	Me		Me		Me	Me	—
26	Me	-		Me		Me	Me	=
27	Me	-		Me		Me	Me	=
28	Me	-		Me		Me	Me	=
29	Me	Me		H	H		H	—



Ex. No.	c	d	e	f	g	h
30		Me		Me	Me	
31	H	Me		Me	Me	
32		Me		Me	Me	Me
33		Me		Me	Me	Me



## Formulation Example 1

	(1) Compound obtained in Example 4	50 mg
	(2) Lactose	34 mg
	(3) Corn starch	10.6 mg
5	(4) Corn starch (paste)	5 mg
	(5) Magnesium stearate	0.4 mg
	(6) Calcium carboxymethyl cellulose	20 mg
	Total	120 mg

10 (1) to (6) were mixed in an ordinary manner, and  
tabletted into tablets using a tableting machine.

## Experimental Example 1

15 Evaluation of cell protective activity against  $\beta$ -  
amyloid neurotoxicity in human neuroblastoma SK-N-SH  
cells

Method

## a) Material Used

20 Human neuroblastoma SK-N-SH cells: obtained from  
American Type Tissue Culture Collection (ATCC).  
DMEM/F-12 medium: obtained from Nikken Biological  
Medicine Laboratory Co.  
Ca<sup>++</sup> and Mg<sup>++</sup> free phosphate-buffered saline (PBS(-  
)): obtained from Nikken Biological Medicine  
25 Laboratory Co.  
N2 supplement <sup>TM</sup>, and EDTA solution: obtained from  
Gibco BRL Co.  
Fetal calf serum, and mixture of penicillin (5000  
U/mL) and streptomycin (5 mg/mL): obtained from Bio  
30 Whittaker Co.  
Recombinant human interferon gamma (rhIFN- $\gamma$ ):  
obtained from Wako Pure Chemical Co.  
Alamar Blue <sup>TM</sup> reagent: obtained from AccuMed  
International, Inc.  
35 Culture flasks: manufactured by Falcon Co.  
Collagen-coated, 96-well multi-plate: manufactured

by Iwaki Glass Co.

$\beta$ -amyloid 25-35: obtained from Bachem AG.

Other reagents: commercially-available special-grade chemicals.

5

b) Test Method

(1) Cultivation of SK-N-SH cells

SK-N-SH cells were sub-cultured in DMEM/F12 medium containing 5 % FCS, 0.5 % N2 supplement <sup>TM</sup>, 1 % of  
10 mixture of penicillin (5000 U/mL) and streptomycin (5 mg/mL), under 10 % CO<sub>2</sub> and 90 % air, using CO<sub>2</sub> incubator. At sub-confluent condition, cells were harvested from culture flask with PBS(-) containing 2.5 mM EDTA, and  
15 plated at a density of  $1.0 \times 10^4$  cells/100  $\mu$ l of culture medium/well in collagen-coated 96-well multi-plate. The next day, 80  $\mu$ l of culture medium was substituted with DMEM/F12 medium (containing neither FCS nor N2 supplement) containing 1.25 ng/mL of rhIFN- $\gamma$ ,  
20 and after 24 hr cultivation cells were used for cell toxicity assay mentioned below.

(2) Measurement of cell protective activity of test compounds against  $\beta$ -amyloid 25-35-induced neurotoxicity

After pretreatment of SK-N-SH cells with rhIFN- $\gamma$   
25 in collagen-coated 96 well multi-plate, cell toxicity assay was started by addition of  $\beta$ -amyloid 25-35 and test compound. Briefly, 80  $\mu$ l of culture medium was removed, and 40  $\mu$ l of  $\beta$ -amyloid 25-35 and 40  $\mu$ l of test compound were added to cultures at the same time.  
30 The final concentrations of  $\beta$ -amyloid 25-35 and test compounds were 10  $\mu$ M and 1  $\mu$ M, respectively.

The test compound was dissolved at 10 mM in dimethylsulfoxide (DMSO) and diluted in DMEM/F12 medium.  $\beta$ -amyloid 25-35 was dissolved at 5 mM in sterile pure  
35 water, and stored at -80°C. Immediately before use,

the stock solution  $\beta$ -amyloid 25-35 was diluted in DMEM/F12 medium and sonicated.

(3) Evaluation of cell protective activity of test compound

Cell viability was assessed by the reduction of Alamar Blue™ reagents, 3 days after starting of the cell toxicity assay. Briefly, 20  $\mu$ l of culture medium was substituted with 20  $\mu$ l of Alamar Blue™ reagents and incubated 4 hours. Absorbances were determined at wavelengths of 570 nm and 600 nm using a plate reader (MTP-32 Micro-plate Reader, manufactured by Corona Co.). Amount of reduced Alamar Blue™ reagents was determined by subtracting absorbance<sub>600</sub> from absorbance<sub>570</sub>. The cell protective activity of the test compound was estimated according to the following equation:

$$\text{Cell protective activity of compound} = [(A-B)/(C-B)] \times 100 (\%)$$

where;

A: cell viability of the group treated with both the test compound and  $\beta$ -amyloid

B: cell viability of the group treated with  $\beta$ -amyloid only

C: cell viability of the control group

Results

Cell viability of the group treated with both the test compound and  $\beta$ -amyloid was compared with that group treated with  $\beta$ -amyloid only using Dunnett's test. Cell viability of each group was determined using at least 4 culture well. The data obtained are shown in the following Table.

Compound of Example	Cell Protecting Activity (%)
1	30.7
2	27.9
3	39.4
7	27.3
12	44.8
14	44.2
25	47.0

These data verify that compound (I) and compound (Ia) well suppress  $\beta$ -amyloid toxicity.

5

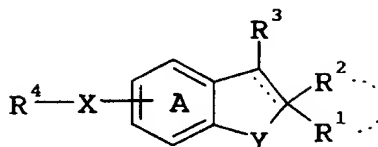
#### INDUSTRIAL APPLICABILITY

Compounds (I) and (Ia) have excellent suppressive effects on neurodegeneration and good permeability to the brain, while having low toxicity, and are therefore useful as medicines for preventing and/or treating neurodegenerative diseases.

10

## CLAIMS

1. A compound of the formula:



- 5 wherein R<sup>1</sup> and R<sup>2</sup> each represents a hydrogen atom or a hydrocarbon group which may be substituted, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted;
- 10 R<sup>3</sup> represents a hydrogen atom, a lower alkyl which may be substituted or an aromatic group which may be substituted;
- R<sup>4</sup> represents (1) an aromatic group which may be substituted, (2) an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (3) an acyl;
- 15 X and Y each represents an oxygen atom or a sulfur atom which may be oxidized;
- 20 ---- represents a single bond or a double bond; and ring A represents a benzene ring which may be further substituted apart from the group of the formula: -X-R<sup>4</sup> wherein each symbol is as defined above, provided that when X and Y are oxygen atoms and ---- is
- 25 a single bond, R<sup>4</sup> is not an acyl, or a salt thereof.
2. A compound of Claim 1, wherein R<sup>1</sup> and R<sup>2</sup> each is
- (i) a hydrogen atom or
- (ii) a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl or C<sub>6-14</sub> aryl group which may be substituted
- 30 by 1 to 5 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7)

optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) C<sub>6-14</sub> aryl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino, (15) mono-C<sub>6-14</sub> arylamino, (16) di-C<sub>1-6</sub> alkylamino, (17) di-C<sub>6-14</sub> arylamino, (18) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (19) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (20) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (22) 5- to 10-membered aromatic heterocyclic group and (23) sulfo, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a C<sub>3-8</sub> cycloalkane or a 3- to 8-membered heterocyclic ring, each of which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl, C<sub>7-16</sub> aralkyl, amino, mono-C<sub>1-6</sub> alkylamino, mono-C<sub>6-14</sub> arylamino, di-C<sub>1-6</sub> alkylamino, di-C<sub>6-14</sub> arylamino and 5- to 10-membered aromatic heterocyclic group;

R<sup>3</sup> is (i) a hydrogen atom,

(ii) a C<sub>1-6</sub> alkyl which may be substituted by 1 to 5 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) C<sub>6-14</sub> aryl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino, (15) mono-C<sub>6-14</sub> arylamino, (16) di-C<sub>1-6</sub> alkylamino, (17) di-C<sub>6-14</sub> arylamino, (18) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (19) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (20) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (21) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (22) 5- to 10-membered aromatic heterocyclic group and (23) sulfo, or (iii) a C<sub>6-14</sub> aryl or a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents

selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy;

R<sup>4</sup> is (i) a C<sub>6-14</sub> aryl or a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally



halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy, (ii) an aliphatic hydrocarbon group selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C<sub>3-6</sub> cycloalkyl, which hydrocarbon group substituted by 1 to 3 C<sub>6-14</sub> aryl or 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally

halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy, which hydrocarbon group may be further substituted by 1 to 5 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) C<sub>6-14</sub> aryl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino, (15) mono-C<sub>6-14</sub> arylamino, (16) di-C<sub>1-6</sub> alkylamino, (17) di-C<sub>6-14</sub> arylamino, (18) acyl selected from the group

consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered  
5 heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl,  
10 (19) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (20) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy,  
15 (21) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (22) 5- to 10-membered aromatic heterocyclic group and (23) sulfo, or  
20 (iii) an acyl of the formula:  $-(C=O)-R^5$ ,  $-(C=O)-OR^5$ ,  $-(C=O)-NR^5R^6$ ,  $-(C=S)-NHR^5$ ,  $-SO_2-R^{5a}$  or  $-SO-R^{5a}$  wherein R<sup>5</sup> is (a) a hydrogen atom,  
25 (b) a C<sub>6-14</sub> aryl or a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents  
30 selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally  
35 halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15)

5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy, or (c) a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl or C<sub>3-6</sub> cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of (1) C<sub>6-14</sub> aryl or 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1') halogen atoms, (2') C<sub>1-3</sub> alkylenedioxy, (3') nitro, (4') cyano, (5') optionally halogenated C<sub>1-6</sub> alkyl, (6') optionally halogenated C<sub>2-6</sub> alkenyl, (7') optionally halogenated C<sub>2-6</sub> alkynyl, (8') optionally halogenated C<sub>3-6</sub> cycloalkyl, (9') optionally halogenated C<sub>1-6</sub> alkoxy, (10') optionally halogenated C<sub>1-6</sub> alkylthio, (11') hydroxy, (12') amino, (13') mono-C<sub>1-6</sub> alkylamino, (14') di-C<sub>1-6</sub> alkylamino, (15') 5- to 7-

membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16') acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17') acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18') acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19') sulfo, (20') C<sub>6-14</sub> aryl and (21') C<sub>6-14</sub> aryloxy, (2) halogen atoms, (3) C<sub>1-3</sub> alkylenedioxy, (4) nitro, (5) cyano, (6) optionally halogenated C<sub>1-6</sub> alkyl, (7) optionally halogenated C<sub>2-6</sub> alkenyl, (8) optionally halogenated C<sub>2-6</sub> alkynyl, (9) optionally halogenated C<sub>3-6</sub> cycloalkyl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino, (15) di-C<sub>1-6</sub> alkylamino, (16) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (17) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle

carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl,

5 (18) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (19) acyloxy selected from the group consisting of C<sub>1-6</sub>

10 alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy and (20) sulfo;

R<sup>5a</sup> is (a) a C<sub>6-14</sub> aryl or a 5- to 14-membered aromatic

15 heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms,

20 (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8) optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally

25 halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-

30 membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-

35 carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub>

alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy, or (b) a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl or C<sub>3-6</sub> cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group consisting of (1) a C<sub>6-14</sub> aryl or 5- to 14-membered aromatic heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1') halogen atoms, (2') C<sub>1-3</sub> alkylenedioxy, (3') nitro, (4') cyano, (5') optionally halogenated C<sub>1-6</sub> alkyl, (6') optionally halogenated C<sub>2-6</sub> alkenyl, (7') optionally halogenated C<sub>2-6</sub> alkynyl, (8') optionally halogenated C<sub>3-6</sub> cycloalkyl, (9') optionally halogenated C<sub>1-6</sub> alkoxy, (10') optionally halogenated C<sub>1-6</sub> alkylthio, (11') hydroxy, (12') amino, (13') mono-C<sub>1-6</sub> alkylamino, (14') di-C<sub>1-6</sub> alkylamino, (15') 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (16') acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub>

alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17') acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18') acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19') sulfo, (20') C<sub>6-14</sub> aryl and (21') C<sub>6-14</sub> aryloxy, (2) halogen atoms, (3) C<sub>1-3</sub> alkylenedioxy, (4) nitro, (5) cyano, (6) optionally halogenated C<sub>1-6</sub> alkyl, (7) optionally halogenated C<sub>2-6</sub> alkenyl, (8) optionally halogenated C<sub>2-6</sub> alkynyl, (9) optionally halogenated C<sub>3-6</sub> cycloalkyl, (10) optionally halogenated C<sub>1-6</sub> alkoxy, (11) optionally halogenated C<sub>1-6</sub> alkylthio, (12) hydroxy, (13) amino, (14) mono-C<sub>1-6</sub> alkylamino, (15) di-C<sub>1-6</sub> alkylamino, (16) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic heterocyclic group, (17) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (18) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub> alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (19) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-



carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy and (20) sulfo; and

R<sup>6</sup> is a hydrogen atom or a C<sub>1-6</sub> alkyl; and

ring A is a benzene ring which may be further

- 5 substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-3</sub> alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C<sub>1-6</sub> alkyl, (6) optionally halogenated C<sub>2-6</sub> alkenyl, (7) optionally halogenated C<sub>2-6</sub> alkynyl, (8)
- 10 optionally halogenated C<sub>3-6</sub> cycloalkyl, (9) optionally halogenated C<sub>1-6</sub> alkoxy, (10) optionally halogenated C<sub>1-6</sub> alkylthio, (11) hydroxy, (12) amino, (13) mono-C<sub>1-6</sub> alkylamino, (14) di-C<sub>1-6</sub> alkylamino, (15) 5- to 7-
- 15 membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-
- 20 membered aromatic heterocyclic group, (16) acyl selected from the group consisting of formyl, carboxy, carbamoyl, C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>6-14</sub> aryl-carbonyl, C<sub>7-16</sub> aralkyl-
- 25 carbonyl, C<sub>6-14</sub> aryloxy-carbonyl, C<sub>7-16</sub> aralkyloxy-carbonyl, 5- or 6-membered heterocycle carbonyl, mono-C<sub>1-6</sub> alkyl-carbamoyl, di-C<sub>1-6</sub> alkyl-carbamoyl, C<sub>6-14</sub> aryl-carbamoyl, 5- or 6-membered heterocycle carbamoyl, C<sub>1-6</sub>
- 30 alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, (17) acylamino selected from the group consisting of formylamino, C<sub>1-6</sub> alkyl-carboxamido, C<sub>6-14</sub> aryl-carboxamido, C<sub>1-6</sub> alkoxy-carboxamido, C<sub>1-6</sub>
- 35 alkylsulfonylamino and C<sub>6-14</sub> arylsulfonylamino, (18) acyloxy selected from the group consisting of C<sub>1-6</sub> alkyl-carbonyloxy, C<sub>6-14</sub> aryl-carbonyloxy, C<sub>1-6</sub> alkoxy-carbonyloxy, mono-C<sub>1-6</sub> alkyl-carbamoyloxy, di-C<sub>1-6</sub> alkyl-carbamoyloxy, C<sub>6-14</sub> aryl-carbamoyloxy and nicotinoyloxy, (19) sulfo, (20) C<sub>6-14</sub> aryl and (21) C<sub>6-14</sub> aryloxy.
3. A compound of Claim 1, wherein R<sup>1</sup> and R<sup>2</sup> each is a C<sub>1-6</sub> alkyl which may be substituted, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a 3- to

8-membered carbo or heterocyclic ring which may be substituted.

4. A compound of Claim 1,  $R^3$  is an aromatic group which may be substituted.

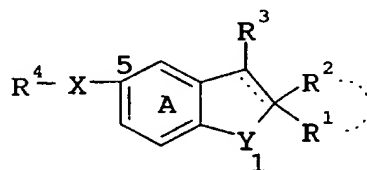
5. A compound of Claim 1, wherein  $R^4$  is (i) an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (ii) an acyl.

6. A compound of Claim 1, wherein X is an oxygen atom.

7. A compound of Claim 1, wherein Y is an oxygen atom.

8. A compound of Claim 7, wherein a group of the formula:  $-X-R^4$  is substituted on the 5-position of the benzofuran ring.

9. A compound of Claim 1, which is a compound of the formula:



wherein each symbol is as defined in Claim 1, or a salt thereof.

10. A compound of Claim 1, wherein  $R^1$  and  $R^2$  each is a  $C_{1-6}$  alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of (1)  $C_{6-14}$  aryl, (2)  $C_{1-6}$  alkoxy, (3)  $C_{1-6}$  alkylthio, (4) hydroxy, (5) amino, (6) mono- $C_{1-6}$  alkylamino, (7) mono- $C_{6-14}$  arylamino, (8) di- $C_{1-6}$  alkylamino, (9) di- $C_{6-14}$  arylamino, (10) carboxy, (11)  $C_{1-6}$  alkylsulfonyl, (12)  $C_{6-14}$  arylsulfonyl, (13)  $C_{1-6}$  alkylsulfinyl, (14)  $C_{6-14}$  arylsulfinyl and (15) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{6-14}$  aryl and 5- to 10-membered aromatic group, or  $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted by 1 to 3 substituents

selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl, C<sub>7-16</sub> aralkyl and 5- to 10-membered aromatic heterocyclic group;

5 R<sup>3</sup> is a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-6</sub> alkyl, (3) C<sub>1-6</sub> alkoxy, (4) mono-C<sub>1-6</sub> alkylamino, (5) di-C<sub>1-6</sub> alkylamino and (6) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic group;

15 R<sup>4</sup> is (i) C<sub>1-6</sub> alkyl substituted by a phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-indolyl or 2-benzothiazolyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of (1) halogen atoms, (2) C<sub>1-6</sub> alkyl, (3) C<sub>1-6</sub> alkoxy, (4) hydroxy, (5) amino, (6) mono-C<sub>1-6</sub> alkylamino, (7) di-C<sub>1-6</sub> alkylamino, (8) carboxy and (9) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and 5- to 10-membered aromatic group, which C<sub>1-6</sub> alkyl may be further substituted by carboxy or C<sub>1-6</sub> alkoxy-carbonyl, or

25 (ii) a C<sub>1-6</sub> alkyl-carbonyl, C<sub>3-6</sub> cycloalkyl-carbonyl, C<sub>6-14</sub> aryl-carbonyl or C<sub>7-16</sub> aralkyl-carbonyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylamino and carboxy;

35 X is an oxygen atom;

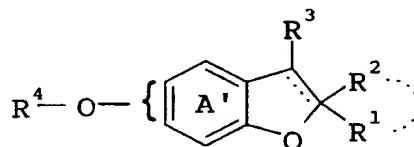
Y is an oxygen atom; and

ring A is a benzene ring which may be further substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C<sub>1-6</sub> alkyl, optionally halogenated C<sub>1-6</sub> alkoxy, amino, mono-C<sub>1-6</sub> alkylamino and di-C<sub>1-6</sub> alkylamino.

11. A compound of Claim 1, wherein R<sup>1</sup> and R<sup>2</sup> each is a C<sub>1-6</sub> alkyl which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>6-14</sub> aryl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, mono-C<sub>6-14</sub> arylamino, di-C<sub>1-6</sub> alkylamino, di-C<sub>6-14</sub> arylamino, carboxy, C<sub>1-6</sub> alkylsulfonyl, C<sub>6-14</sub> arylsulfonyl, C<sub>1-6</sub> alkylsulfinyl and C<sub>6-14</sub> arylsulfinyl, or
- 15 R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a piperidine which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>6-14</sub> aryl and C<sub>7-16</sub> aralkyl;
- R<sup>3</sup> is a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, amino, mono-C<sub>1-6</sub> alkylamino and di-C<sub>1-6</sub> alkylamino;
- 20 R<sup>4</sup> is (i) C<sub>1-6</sub> alkyl substituted by a phenyl or pyridyl, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylamino and carboxy, or
- 25 (ii) an acyl of the formula: -(C=O)-R<sup>5'</sup> wherein R<sup>5'</sup> is a phenyl or phenyl-C<sub>1-6</sub> alkyl, each of which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxy, amino, mono-C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylamino and carboxy;
- 30 X is an oxygen atom;
- 35 Y is an oxygen atom; and
- ring A is a benzene ring which may be further

substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C<sub>1-6</sub> alkyl, optionally halogenated C<sub>1-6</sub> alkoxy, amino, mono-C<sub>1-6</sub> alkylamino and di-C<sub>1-6</sub> alkylamino.

12. A compound of Claim 1 which is a compound of the formula:



wherein R<sup>1</sup> and R<sup>2</sup> each is C<sub>1-6</sub> alkyl which may be substituted by 6-membered saturated cyclic amino substituted by a phenyl, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a piperidine substituted by a C<sub>1-6</sub> alkyl or a C<sub>7-16</sub> aralkyl;

R<sup>3</sup> is (i) a hydrogen atom, or (ii) a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of (1) C<sub>1-6</sub> alkyl, (2) di-C<sub>1-6</sub> alkylamino and (3) 6-membered saturated cyclic amino which may be substituted by a C<sub>1-6</sub> alkyl,

R<sup>4</sup> is (i) a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of nitro and C<sub>1-6</sub> alkyl-carboxamido, (ii) a C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkenyl group substituted by 1 to 3 of phenyl, quinolyl or pyridyl, each of which may be substituted by 1 to 3 substituents selected from the group consisting of C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>1-6</sub> alkylsulfonyl and C<sub>1-6</sub> alkylsulfinyl, which C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkenyl group may be further substituted by a phenyl, carboxy or C<sub>1-6</sub> alkoxy-carbonyl, or

(iii) an acyl of the formula: -(C=O)-R<sup>5''</sup> wherein R<sup>5''</sup> is phenyl substituted by a C<sub>1-6</sub> alkoxy; and

ring A' is a benzene ring which may be further substituted by 1 to 3 C<sub>1-6</sub> alkyl.

13. A compound of Claim 1 which is

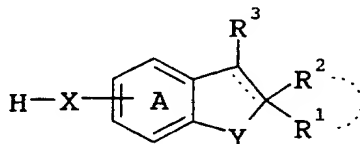
3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran,

3-(4-isopropylphenyl)-2,4,6,7-tetramethylbenzofuran-5-yl 4-methoxybenzoate,

3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-2,4,6,7-tetramethylbenzofuran,

3-(4-isopropylphenyl)-5-(4-methoxybenzyloxy)-1',4,6,7-tetramethylspiro[benzofuran-2(3H),4'-piperidine], or a salt thereof.

14. A process for producing of a compound of Claim 1, which comprises reacting a compound of the formula:



wherein each symbol is as defined in Claim 1, or a salt thereof with a compound of the formula: R<sup>4</sup>-L wherein L represents a leaving group and R<sup>4</sup> is as defined in Claim 1, or salt thereof.

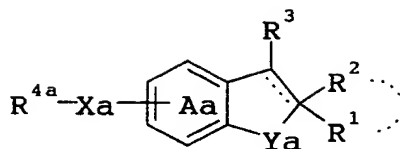
15. A pharmaceutical composition which comprises a compound of Claim 1.

16. A composition of Claim 15 which is an agent for suppressing neurodegeneration.

17. A composition of Claim 15 which is an agent for suppressing  $\beta$ -amyloid toxicity.

18. A composition of Claim 15 which is an agent for preventing and/or treating neurodegenerative diseases.

19. An agent for preventing and/or treating neurodegenerative diseases which comprises a compound of the formula:



wherein R<sup>1</sup> and R<sup>2</sup> each represents a hydrogen atom or a hydrocarbon group which may be substituted, or R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted;

R<sup>3</sup> represents a hydrogen atom, a lower alkyl which may be substituted or an aromatic group which may be substituted;

R<sup>4a</sup> represents an aromatic group which may be substituted, an aliphatic hydrocarbon group which may be substituted or an acyl;

Xa represents an oxygen atom or a sulfur atom which may be oxidized;

Ya represents an oxygen atom, a sulfur atom which may be oxidized or an imino which may be substituted;

---- represents a single bond or a double bond;

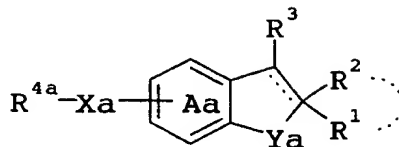
ring Aa represents a benzene ring which may be further substituted apart from (i) the group of the formula:

-Xa-R<sup>4a</sup> wherein each symbol is as defined above, and (ii) an amino which may be substituted, provided that when Xa and Ya are oxygen atoms and ---- is a single bond, R<sup>4</sup> is not an acyl, or a salt thereof.

20. An agent of Claim 19 which is an agent for suppressing  $\beta$ -amyloid toxicity.

21. An agent of Claim 19 which is an agent for preventing and/or treating neurodegenerative diseases.

22. A method for suppressing neurodegeneration in mammal, which comprises administering to said mammal an effective amount of a compound of the formula:



wherein  $R^1$  and  $R^2$  each represents a hydrogen atom or a hydrocarbon group which may be substituted, or  $R^1$  and  $R^2$  form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted;

$R^3$  represents a hydrogen atom, a lower alkyl which may be substituted or an aromatic group which may be substituted;

$R^{4a}$  represents an aromatic group which may be substituted, an aliphatic hydrocarbon group which may be substituted or an acyl;

Xa represents an oxygen atom or a sulfur atom which may be oxidized;

Ya represents an oxygen atom, a sulfur atom which may be oxidized or an imino which may be substituted;

---- represents a single bond or a double bond;

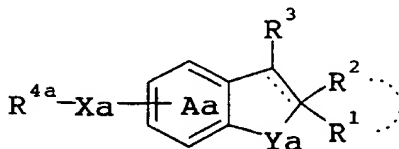
ring Aa represents a benzene ring which may be further substituted apart from (i) the group of the formula:

-Xa- $R^{4a}$  wherein each symbol is as defined above, and (ii) an amino which may be substituted,

provided that when Xa and Ya are oxygen atoms and ---- is a single bond,  $R^4$  is not an acyl,

or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable excipient, carrier or diluent.

23. Use of a compound of the formula:



wherein  $R^1$  and  $R^2$  each represents a hydrogen atom or a hydrocarbon group which may be substituted, or



R<sup>1</sup> and R<sup>2</sup> form, taken together with the adjacent carbon atom, a 3- to 8-membered carbo or heterocyclic ring which may be substituted;

5 R<sup>3</sup> represents a hydrogen atom, a lower alkyl which may be substituted or an aromatic group which may be substituted;

R<sup>4a</sup> represents an aromatic group which may be substituted, an aliphatic hydrocarbon group which may be substituted or an acyl;

10 Xa represents an oxygen atom or a sulfur atom which may be oxidized;

Ya represents an oxygen atom, a sulfur atom which may be oxidized or an imino which may be substituted;

---- represents a single bond or a double bond;

15 ring Aa represents a benzene ring which may be further substituted apart from (i) the group of the formula:

-Xa-R<sup>4a</sup> wherein each symbol is as defined above, and (ii) an amino which may be substituted,

provided that when Xa and Ya are oxygen atoms and ----  
20 is a single bond, R<sup>4</sup> is not an acyl,  
or a salt thereof for manufacturing a pharmaceutical composition for suppressing neurodegeneration.



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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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			(43) International Publication Date: 10 December 1998 (10.12.98)
(21) International Application Number: PCT/JP98/02482 (22) International Filing Date: 4 June 1998 (04.06.98) (30) Priority Data: 9/148325 5 June 1997 (05.06.97) JP (71) Applicant (for all designated States except US): TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): OHKAWA, Shigenori [JP/JP]; 45-20, Makamicho 6-chome, Takatsuki-shi, Osaka 569-1121 (JP). SETOH, Masaki [JP/JP]; 18-D73-302, Tsukumodai 5-chome, Suita-shi, Osaka 565-0862 (JP). KAKIHANA, Mitsuru [JP/JP]; 4-2, Tsukushigaoka 9-chome, Kita-ku, Kobe-shi, Hyogo 651-1212 (JP). OKURA, Masahiro [JP/JP]; 6-3-A, Shibuya 2-chome, Ikeda-shi, Osaka 563-0028 (JP). (74) Agents: ASAHINA, Tadao et al.; Osaka Plant of Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-0024 (JP).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. (88) Date of publication of the international search report: 4 March 1999 (04.03.99)	
(54) Title: BENZOFURANS AND BENZOTHOPIHENES AS SUPPRESSORS OF NEURODEGENERATION			
<div style="text-align: center;"> <p>(I)</p> </div>			
(57) Abstract <p>A compound of formula (I): wherein R<sup>1</sup> and R<sup>2</sup> each is H or a hydrocarbon group which may be substituted, or R<sup>1</sup> and R<sup>2</sup> form a 3- to 8-membered carbo or heterocyclic ring which may be substituted; R<sup>3</sup> is H, a lower alkyl which may be substituted or an aromatic group which may be substituted; R<sup>4</sup> is (1) an aromatic group which may be substituted, (2) an aliphatic hydrocarbon group substituted by an aromatic group which may be substituted, which hydrocarbon group may be further substituted or (3) an acyl; X and Y each is oxygen or sulfur which may be oxidized; and ring A is a benzene ring which may be further substituted, or a salt thereof, is useful for an agent for suppressing neurodegeneration.</p>			

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## INTERNATIONAL SEARCH REPORT

Internat'l Application No  
PCT/JP 98/02482

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/79 C07D307/81 C07D405/06 C07D413/06 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

30 October 1998

Date of mailing of the international search report

02.12.98

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Intern      Application No  
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Intern. Patent Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 98/02482

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1-12, 14-23 (all partly)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Claims Nos.: 1-12,14-23(all partly)

The open-ended definitions given in the claims are too general and/or encompass too broad a range of totally different chemical groups, only partly supported by examples given in the specification. In view of the exceedingly large number of compounds which are defined by these definitions the search had to be limited to the compounds for which experimental data was given and/or the compounds mentioned in the claims and to the general idea underlying the application. (see Guidelines, Chapter III, paragraph 2.3). However, as the number of documents disclosing compounds which fall under the scope of the present claims still amounts to several hundreds a selection of relevant patent documents is only cited.

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Information on patent family members

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/02482

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/02482

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/02482

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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## PATENT COOPERATION TREATY

COPIED FOR COMPUTER

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

To:

ELKINGTON & FIFE  
Prospect House  
Attn. Hall, Marina  
8 Pembroke Road  
Sevenoaks  
Kent TN13 1XR  
UNITED KINGDOM

RECEIVED

3 DEC 1998

ELKINGTON &amp; FIFE SEVENOAKS

Date of mailing  
(day/month/year)

02. 12. 98

Applicant's or agent's file reference

2470WOOP MH/99850PC

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/JP 98/02482

International filing date  
(day/month/year)

04/06/1998

Applicant

TAKEDA CHEMICAL INDUSTRIES, LTD. et al.

- 1.
- ☒
- The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

- 2.
- ☐
- The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

- 3.
- ☐
- With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

- 4.
- Further action(s):**
- The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Wolfgang Borinski

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

**The following examples illustrate the manner in which amendments must be explained in the accompanying letter:**

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### **"Statement under article 19(1)" (Rule 46.4)**

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### **Consequence if a demand for international preliminary examination has already been filed**

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### **Consequence with regard to translation of the international application for entry into the national phase**

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>2470W00P</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/JP 98/ 02482</b>	International filing date (day/month/year) <b>04/06/1998</b>	(Earliest) Priority Date (day/month/year) <b>05/06/1997</b>
Applicant <b>TAKEDA CHEMICAL INDUSTRIES, LTD. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 11 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
- ☐ filed with the international application.
  - ☐ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant.  
☒ the text has been established by this Authority to read as follows:

**BENZOFURANS AND BENZOTHPHENES AS SUPPRESSORS OF NEURODEGENERATION**

5. With regard to the abstract,
- ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. ////

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 98/02482

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1-12, 14-23 (all partly)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1-12,14-23(all partly)

The open-ended definitions given in the claims are too general and/or encompass too broad a range of totally different chemical groups, only partly supported by examples given in the specification. In view of the exceedingly large number of compounds which are defined by these definitions the search had to be limited to the compounds for which experimental data was given and/or the compounds mentioned in the claims and to the general idea underlying the application. (see Guidelines, Chapter III, paragraph 2.3). However, as the number of documents disclosing compounds which fall under the scope of the present claims still amounts to several hundreds a selection of relevant patent documents is only cited.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/02482

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/79 C07D307/81 C07D405/06 C07D413/06 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<input checked="" type="checkbox"/>	CHEMICAL ABSTRACTS, vol. 110, no. 19, 8 May 1989 Columbus, Ohio, US; abstract no. 173099g, page 762; XP002074285 see abstract & CN 88 100 659 A (MITSUI PETROCHEMICAL INDUSTRIES) 14 September 1988 --- -/-	1-12, 14

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

30 October 1998

Date of mailing of the international search report

02. 12. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Herz, C

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/02482

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
✓ X	CHEMICAL ABSTRACTS, vol. 126, no. 17, 28 April 1997 Columbus, Ohio, US; abstract no. 225226y, page 570; XP002074286 see abstract & ZA 9 509 262 A (ABBOTT LABORATORIES) 29 May 1996 <i>not an x</i>	1-12,14
✓ P,X	DE 196 02 095 A (BAYER AG) 24 July 1997 see claim 1; example 42	1-12,14
✓ X	PATENT ABSTRACTS OF JAPAN vol. 096, no. 001, 31 January 1996 & JP 07 247263 A (NIPPON SODA CO., LTD.), 26 September 1995 see abstract	1-12,14
✓ X	US 4 659 360 A (J. S. BAUM, T. M. CHEN) 21 April 1987 see claim 1; examples 100,101	1-12,14
X	EP 0 165 810 A (MERCK FROSST CANADA INC.) 27 December 1985 see claim 1; example 34A	1-12,14
X	US 4 426 385 A (P. A. CAIN) 17 January 1984 see column 15, line 20-21	1-12,14
X	EP 0 054 924 A (THE WELLCOME FOUNDATION LTD.) 30 June 1982 * Compounds of formula V * see example 5A	1-12,14
P,X	US 5 681 842 A (J. F. DELLARIA, T. H. GANE) 28 October 1997 see claim 1; example 3	1-12,14
✓ X	EP 0 733 631 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 25 September 1996 see claim 1	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 095, no. 009, 31 October 1995 & JP 07 145147 A (YAMANOUCHI PHARMACEUT. CO., LTD.), 6 June 1995 see abstract	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 095, no. 002, 31 March 1995 & JP 06 312976 A (YAMANOUCHI PHARMACEUT. CO., LTD.), 8 November 1994 see abstract	1-12,14
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/02482

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 015, no. 392, 4 October 1991 & JP 03 161405 A (MITSUI PETROCHEM. IND., LTD.), 11 July 1991 see abstract ---	1-12,14
X	EP 0 394 043 A (SUMITOMO CHEMICAL COMPANY, LIMITED) 24 October 1990 see claim 1; examples 1-619 ---	1-12,14
X	EP 0 365 925 A (MITSUBISHI KASEI CORPORATION) 2 May 1990 see claim 1; example 67 ---	1-12,14
X	EP 0 729 956 A (ELI LILLY AND COMPANY) 4 September 1996 * Examples * see claim 1 ---	1-12,14
X	WO 91 05474 A (MITSUI PETROCHEMICAL INDUSTRIES, LTD.) 2 May 1991 see claim 1 ---	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 015, no. 377, 24 September 1991 & JP 03 151311 A (MITSUI PETROCHEM. IND., LTD.), 27 June 1991 see abstract ---	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 016, no. 066, 19 February 1992 & JP 03 261778 A (KOTOBUKI SEIYAKU K. K.), 21 November 1991 see abstract ---	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 016, no. 518, 26 October 1992 & JP 04 193803 A (MITSUI PETROCHEM. IND. LTD.), 13 July 1992 see abstract ---	1-12,14
X	EP 0 526 951 A (SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B. V.) 10 February 1993 see claim 1; example 76 ---	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 018, no. 625, 29 November 1994 & JP 06 239853 A (MITSUI PETROCHEM. IND. LTD.), 30 August 1994 see abstract ---	1-12,14
X	WO 95 09159 A (OTSUKA PHARMACEUTICAL CO., LTD.) 6 April 1995 see claim 1 ---	1-12,14
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/02482

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 095, no. 010, 30 November 1995 & JP 07 179856 A (CANON K. K.), 18 July 1995 * page 8, scheme B; page 9, groups Cm2, Ha1, Ha2, Hb1, Hb2 * see abstract; claim 1 ---	1-12,14
P,X	WO 97 34869 A (EISAI CO., LTD.) 25 September 1997 see claim 3; example 41 ---	1-12,14
X	WO 95 29907 A (FUJISAWA PHARMACUTICAL CO., LTD.) 9 November 1995 see claim 1; examples 10-1,10-2 ---	1-12,14
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Y	WO 95 17095 A (ELI LILLY AND COMPANY) 29 June 1995 cited in the application see page 6, line 16 - page 7, line 2; claims 1-7 ---	1-23
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/02482

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Y	EP 0 383 281 A (TOYAMA CHEMICAL CO., LTD.) 22 August 1990 see claims 1,18 ---	1-23
X	WO 96 10999 A (G. D. SEARLE & CO.) 18 April 1996 see claim 1 ---	1-12,14
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X	--- M. SHIPCHANDLER ET AL.: "Coumarins. XI. Total synthesis of (+/-)-columbianetin" J. PHARM. SCI., vol. 59, no. 1, 1970, pages 67-71, XP002082810 * Scheme I, II *	1-12,14
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International Application No

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	J. S. KALTENBRONN ET AL.: "Benzofuran derivatives as ET(A)-selective, non-peptide endothelin antagonists" EUR. J. MED. CHEM., vol. 32, no. 5, 1997, pages 425-431, XP002082812 see tables I,II -----	1-12,14

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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

## PCT

To:

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**E. & F. SEVENOAKS**

### NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

**08.09.99**

Applicant's or agent's file reference  
**MH/F9985OPC**

#### IMPORTANT NOTIFICATION

International application No.  
**PCT/JP98/02482**

International filing date (day/month/year)  
**04/06/1998**

Priority date (day/month/year)  
**05/06/1997**

Applicant

**TAKEDA CHEMICAL INDUSTRIES, LTD. et al.**

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>MH/F9985OPC</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/JP98/02482</b>	International filing date (day/month/year) <b>04/06/1998</b>	Priority date (day/month/year) <b>05/06/1997</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D307/79</b>		
Applicant <b>TAKEDA CHEMICAL INDUSTRIES, LTD. et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  <b>18/12/1998</b>	Date of completion of this report  <b>08.09.99</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b> <b>Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>Herz, C</b>  Telephone No. <b>+49 89 2399 8275</b> 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP98/02482

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-109 as originally filed

**Claims, No.:**

1-23 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 1-12, 14-23.

because:

- ☒ the said international application, or the said claims Nos. 22 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP98/02482

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-12,14-21,23(all part).

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	13,15-21,23
	No:	Claims	1-12,14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21,23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

**2. Citations and explanations**

see separate sheet

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

see separate sheet

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP98/02482

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**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/JP98/02482

1. The Applicant is informed that this Report is based on the documents retrieved by the search. Due to the fact that this search was not carried out completely for all claims, since the scope of the claims was too broadly formulated this Report cannot be complete.
2. Claim 22 is directed to a therapeutical method performed on humans. Under the terms of Rule 67.1 (iv) PCT, the International Preliminary Examination Authority is not required to carry out an examination on such claim.
3. The priority documents pertaining to the present application were not available at the time of establishing this Report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct the following documents cited in the International Search Report could become relevant in order to assess whether the claims satisfy the criteria set forth in Article 33 (1) PCT: DE-A-196 02 095, US-A-5 681 842, WO-A-97 34869, EP-A-0 778 274, WO-A-97 25033, WO-A-98 05292.
4. The group of compounds claimed in the present application is anticipated by the compounds disclosed in the documents classified "X" in the International Search Report.
5. With regard to the presence of inventive step reference is made to the documents classified "X" and "Y" in the ISER wherein the same or similar compounds possessing the capability to suppress neurodegeneration have been disclosed. Substituents therein are the same as or similar to those given in the present application.

Taking into account these facts the man skilled in the art would have to expect the neurodegeneration suppressing capability without affecting their basic capabilities when modifying the basic moiety and/or the substituents of the groups of compounds disclosed in the state of the art. Thus representing only predictable effects the compounds claimed are considered to be obvious.

Consequently, Claims 1 to 21 and 23 are also lacking inventive step under Article 33 (3) PCT.

6. The use of the terms "aromatic group; substituted; hydrocarbon group; cyclic urea; heterocyclic ring; lower alkyl; acyl" and their compositions throughout the claims without further definitive qualification therein renders these claims obscure in scope in that it does not indicate any specific substituents. As chemical species can be precisely defined by the identity and number of atoms involved (cf. the definitions given on pages 27 to 41) the above terms are considered to render these claims obscure in scope in that it does not indicate any specific substituents. Therefore it is not clear whether the compounds implied fall within the scope of the claims of the present application and/or constitute a solution to the problem underlying the application; the incorporation of the specific substituents given in the specification is therefore necessary (Articles 6, 33 (3) PCT).

## PATENT COOPERATION TREATY

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

COPIED FOR COMPUTER

PCT

WRITTEN OPINION

(PCT Rule 66)

To:

HALL, Marina et al  
ELKINGTON & FIFE  
Prospect House  
8 Pembroke Road  
Sevenoaks  
Kent TN13 1XR  
GRANDE BRETAGNE

RECEIVED

15 MAY 1999

E. &amp; F. SEVENOAKS

Date of mailing  
(day/month/year)

11. 05. 99

Applicant's or agent's file reference

MH/F9985OPC

REPLY DUE

within 3 month(s)  
from the above date of mailing

International application No.

PCT/JP98/02482

International filing date (day/month/year)

04/06/1998

Priority date (day/month/year)

05/06/1997

International Patent Classification (IPC) or both national classification and IPC

C07D307/79

Applicant

TAKEDA CHEMICAL INDUSTRIES, LTD. et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☒ Certain document cited
  - VII ☐ Certain defects in the international application
  - VIII ☒ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

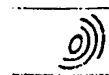
**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 05/10/1999.

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80298 Munich  
Tel. (+49-89) 2399-0 Tx: 523656 epmu d  
Fax: (+49-89) 2399-4465

Authorized officer / Examiner

Herz, C

Formalities officer (incl. extension of time limits)

Ambroa, J.R.

Telephone No. (+49-89) 2399 8012



## WRITTEN OPINION

International application No. PCT/JP98/02482

### I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

**Description, pages:**

1-109 as originally filed

**Claims, No.:**

1-23 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,  
☒ claims Nos. 1-12, 14-23,

because:

- ☒ the said international application, or the said claims Nos. 22 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separat sh et

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

## WRITTEN OPINION

International application No. PCT/JP98/02482

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-12,14-21,23(all part).

### V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### 1. Statement

Novelty (N)	Claims	1-12,14
Inventive step (IS)	Claims	1-21,23
Industrial applicability (IA)	Claims	

#### 2. Citations and explanations

see separate sheet

### VI. Certain documents cited

#### 1. Certain published documents (Rule 70.10)

and / or

#### 2. Non-written disclosures (Rule 70.9)

see separate sheet

### VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet



**WRITTEN OPINION  
SEPARATE SHEET**

International application No. PCT/JP98/02482

1. The Applicant is informed that this Opinion is based on the documents retrieved by the search. Due to the fact that this search was not carried out completely for all claims, since the scope of the claims was too broadly formulated this Opinion cannot be complete.
2. Claim 22 is directed to a therapeutical method performed on humans. Under the terms of Rule 67.1 (iv) PCT, the International Preliminary Examination Authority is not required to carry out an examination on such claim.
3. The priority documents pertaining to the present application were not available at the time of establishing this Opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct the following documents cited in the International Search Report could become relevant in order to assess whether the claims satisfy the criteria set forth in Article 33 (1) PCT: DE-A-196 02 095, US-A-5 681 842, WO-A-97 34869, EP-A-0 778 274, WO-A-97 25033, WO-A-98 05292. // 後願
4. The group of compounds claimed in the present application is anticipated by the compounds disclosed in the documents classified "X" in the International Search Report.

If in view of the overwhelming amount of novelty-destroying material the Applicant is able to define any new subject-matter within the meaning of Art. 33 (2) PCT he is also requested to indicate in which respect the claimed process is inventive.

As being generally deficient under Art. 33 (1) PCT a detailed examination has not yet been carried out on the present application at this time.

5. With regard to the presence of inventive step reference is made to the documents classified "X" and "Y" in the ISER wherein the same or similar compounds possessing the capability to suppress neurodegeneration have been disclosed. Substituents therein are the same as or similar to those given in the present application.

Taking into account these facts the man skilled in the art would have to expect the neurodegeneration suppressing capability without affecting their basic capabilities when modifying the basic moiety and/or the substituents of the groups of compounds disclosed in the state of the art. Thus representing only predictable effects the compounds claimed are considered to be obvious.

Consequently, at present, Claims 1 to 21 and 23 are also lacking inventive step under Article 33 (3) PCT.

Accordingly it is to be demonstrated wherein the inventive step lies in the compounds claimed, e.g. by showing a significant improvement in the property relevant to the solution of the stated problem. If it is chosen to give evidence using comparative tests, these must be carried out in respect of the closest state of the art.

6. The use of the terms "aromatic group; substituted; hydrocarbon group; cyclic urea; heterocyclic ring; lower alkyl; acyl" and their compositions throughout the claims without further definitive qualification therein renders these claims obscure in scope in that it does not indicate any specific substituents. As chemical species can be precisely defined by the identity and number of atoms involved (cf. the definitions given on pages 27 to 41) the above terms are considered to render these claims obscure in scope in that it does not indicate any specific substituents. Therefore it is not clear whether the compounds implied fall within the scope of the claims of the present application and/or constitute a solution to the problem underlying the application; the incorporation of the specific substituents given in the specification is therefore necessary (Articles 6, 33 (3) PCT).

## PATENT COOPERATION TREATY

PCT

REC'D 13 SEP 1999

WIPO PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MH/F9985OPC	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/JP98/02482	International filing date (day/month/year) 04/06/1998	Priority date (day/month/year) 05/06/1997
International Patent Classification (IPC) or national classification and IPC C07D307/79		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 18/12/1998	Date of completion of this report 08.09.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer H rz, C Telephone No. +49 89 2399 8275 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP98/02482

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-109 as originally filed

**Claims, No.:**

1-23 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 1-12, 14-23.

because:

- ☒ the said international application, or the said claims Nos. 22 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP98/02482

**s e s parat sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-12,14-21,23(all part).

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	13,15-21,23
	No:	Claims	1-12,14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21,23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

**2. Citations and explanations**

**see separate sheet**

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP98/02482

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**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/JP98/02482

1. The Applicant is informed that this Report is based on the documents retrieved by the search. Due to the fact that this search was not carried out completely for all claims, since the scope of the claims was too broadly formulated this Report cannot be complete.
2. Claim 22 is directed to a therapeutical method performed on humans. Under the terms of Rule 67.1 (iv) PCT, the International Preliminary Examination Authority is not required to carry out an examination on such claim.
3. The priority documents pertaining to the present application were not available at the time of establishing this Report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct the following documents cited in the International Search Report could become relevant in order to assess whether the claims satisfy the criteria set forth in Article 33 (1) PCT: DE-A-196 02 095, US-A-5 681 842, WO-A-97 34869, EP-A-0 778 274, WO-A-97 25033, WO-A-98 05292.
4. The group of compounds claimed in the present application is anticipated by the compounds disclosed in the documents classified "X" in the International Search Report.
5. With regard to the presence of inventive step reference is made to the documents classified "X" and "Y" in the ISER wherein the same or similar compounds possessing the capability to suppress neurodegeneration have been disclosed. Substituents therein are the same as or similar to those given in the present application.

Taking into account these facts the man skilled in the art would have to expect the neurodegeneration suppressing capability without affecting their basic capabilities when modifying the basic moiety and/or the substituents of the groups of compounds disclosed in the state of the art. Thus representing only predictable effects the compounds claimed are considered to be obvious.

Consequently, Claims 1 to 21 and 23 are also lacking inventive step under Article 33 (3) PCT.

6. The use of the terms "aromatic group; substituted; hydrocarbon group; cyclic urea; heterocyclic ring; lower alkyl; acyl" and their compositions throughout the claims without further definitive qualification therein renders these claims obscure in scope in that it does not indicate any specific substituents. As chemical species can be precisely defined by the identity and number of atoms involved (cf. the definitions given on pages 27 to 41) the above terms are considered to render these claims obscure in scope in that it does not indicate any specific substituents. Therefore it is not clear whether the compounds implied fall within the scope of the claims of the present application and/or constitute a solution to the problem underlying the application; the incorporation of the specific substituents given in the specification is therefore necessary (Articles 6, 33 (3) PCT).

# INTERNATIONAL COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>2470W00P</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/JP 98/ 02482</b>	International filing date (day/month/year) <b>04/06/1998</b>	(Earliest) Priority Date (day/month/year) <b>05/06/1997</b>
Applicant <b>TAKEDA CHEMICAL INDUSTRIES, LTD. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 11 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).
2. ☐ **Unity of invention is lacking** (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
  - ☐ filed with the international application.
  - ☐ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority

4. With regard to the **title**,
  - ☐ the text is approved as submitted by the applicant.
  - ☒ the text has been established by this Authority to read as follows:

**BENZOFURANS AND BENZOTHOPHENES AS SUPPRESSORS OF NEURODEGENERATION**

5. With regard to the **abstract**,
  - ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box II. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. ////

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

☐ None of the figures.



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 98/02482

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1-12, 14-23 (all partly)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1-12,14-23(all partly)

The open-ended definitions given in the claims are too general and/or encompass too broad a range of totally different chemical groups, only partly supported by examples given in the specification. In view of the exceedingly large number of compounds which are defined by these definitions the search had to be limited to the compounds for which experimental data was given and/or the compounds mentioned in the claims and to the general idea underlying the application. (see Guidelines, Chapter III, paragraph 2.3). However, as the number of documents disclosing compounds which fall under the scope of the present claims still amounts to several hundreds a selection of relevant patent documents is only cited.

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/JP 98/02482

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/79 C07D307/81 C07D405/06 C07D413/06 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 110, no. 19, 8 May 1989 Columbus, Ohio, US; abstract no. 173099g, page 762; XP002074285 see abstract & CN 88 100 659 A (MITSUI PETROCHEMICAL INDUSTRIES) 14 September 1988 --- -/--	1-12,14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 October 1998

Date of mailing of the international search report

02. 12. 98

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Herz, C

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/02482

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 126, no. 17, 28 April 1997 Columbus, Ohio, US; abstract no. 225226y, page 570; XP002074286 see abstract & ZA 9 509 262 A (ABBOTT ALBORATORIES) 29 May 1996	1-12,14
P,X	DE 196 02 095 A (BAYER AG) 24 July 1997 see claim 1; example 42	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 096, no. 001, 31 January 1996 & JP 07 247263 A (NIPPON SODA CO., LTD.), 26 September 1995 see abstract	1-12,14
X	US 4 659 360 A (J. S. BAUM, T. M. CHEN) 21 April 1987 see claim 1; examples 100,101	1-12,14
X	EP 0 165 810 A (MERCK FROSST CANADA INC.) 27 December 1985 see claim 1; example 34A	1-12,14
X	US 4 426 385 A (P. A. CAIN) 17 January 1984 see column 15, line 20-21	1-12,14
X	EP 0 054 924 A (THE WELLCOME FOUNDATION LTD.) 30 June 1982 * Compounds of formula V * see example 5A	1-12,14
P,X	US 5 681 842 A (J. F. DELLARIA, T. H. GANE) 28 October 1997 see claim 1; example 3	1-12,14
X	EP 0 733 631 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 25 September 1996 see claim 1	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 095, no. 009, 31 October 1995 & JP 07 145147 A (YAMANOUCHI PHARMACEUT. CO., LTD.), 6 June 1995 see abstract	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 095, no. 002, 31 March 1995 & JP 06 312976 A (YAMANOUCHI PHARMACEUT. CO., LTD.), 8 November 1994 see abstract	1-12,14
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/02482

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 015, no. 392, 4 October 1991 & JP 03 161405 A (MITSUI PETROCHEM. IND., LTD.), 11 July 1991 see abstract ---	1-12,14
X	EP 0 394 043 A (SUMITOMO CHEMICAL COMPANY, LIMITED) 24 October 1990 see claim 1; examples 1-619 ---	1-12,14
X	EP 0 365 925 A (MITSUBISHI KASEI CORPORATION) 2 May 1990 see claim 1; example 67 ---	1-12,14
X	EP 0 729 956 A (ELI LILLY AND COMPANY) 4 September 1996 * Examples * see claim 1 ---	1-12,14
X	WO 91 05474 A (MITSUI PETROCHEMICAL INDUSTRIES, LTD.) 2 May 1991 see claim 1 ---	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 015, no. 377, 24 September 1991 & JP 03 151311 A (MITSUI PETROCHEM. IND., LTD.), 27 June 1991 see abstract ---	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 016, no. 066, 19 February 1992 & JP 03 261778 A (KOTOBUKI SEIYAKU K. K.), 21 November 1991 see abstract ---	1-12,14
X	PATENT ABSTRACTS OF JAPAN vol. 016, no. 518, 26 October 1992 & JP 04 193803 A (MITSUI PETROCHEM. IND. LTD.), 13 July 1992 see abstract ---	1-12,14
X	EP 0 526 951 A (SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B. V.) 10 February 1993 see claim 1; example 76 ---	1-12,14
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